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New approaches to the catalytic activation of arenes and carbonyls

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New approaches to the catalytic activation of arenes and carbonyls

Helen Victoria Lomax

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

November 2015

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Abbreviations

[O]	Oxidation
°C	Degrees centigrade
Å	Angstrom
Ac	Acetyl
Ad	Adamantyl
Aq.	Aqueous
Ar	Aryl
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
Boc	<i>tert</i> -Butyloxycarbonyl
Bu	Butyl
calcd	Calculated
Cat.	Catalyst
Cbz	Benzyl carbamates
CH ₃ CN	Acetonitrile
cod	Cyclooctadiene
Conv.	Conversion
Cp	Cyclopentadienyl
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
Cp*H	1,2,3,4,5-Pentamethylcyclopentadiene
CPME	Cyclopentylmethylether
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide

DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DPPent	1,3-Bis(diphenylphosphino)pentane
E	Electrophile
ee	Enantiomeric excess
Equiv	Equivalents
Et	Ethyl
FG	Functional group
h	Hour
HOBt	Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
IPA	Isopropyl alcohol
L	Ligand
LUMO	Lowest unoccupied molecular orbital
M	Metal
M	Molar
<i>m</i> -	Meta
Me	Methyl
mg	Milligram
MHz	Megahertz
mL	Millilitre
mmol	Millimole
Mol%	Mole percent
MPa	Megapascals
MS	Molecular sieves
MW	Microwave
N	Normal
NBS	<i>N</i> -Bromosuccinimide
NMP	<i>N</i> -Methyl-2-pyrrolidone

NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NR	No reaction
Nuc	Nucleophile
<i>o</i> -	Ortho
OMS	Octahedral molecular sieves
<i>p</i> -	Para
PCC	Pyridinium chlorochromate
PEG	Polyethylene glycol
Ph	Phenyl
PhMe	Toluene
PMP	<i>p</i> -Methoxyphenyl
Pr	Propyl
rt	Room temperature
S _E Ar	Electrophilic aromatic substitution
S _N Ar	Nucleophilic aromatic substitution
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -Tetraaryl-1,3-dioxolan-4,5-dimethanol
TBSO	<i>tert</i> -Butyldimethylsilyl ethers
<i>t</i> -Bu	Tertiary butyl
Tf	Triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSCN	Trimethylsilyl cyanide
μ L	Microlitre

Abstract

The activation of styrene towards nucleophilic addition and a Diels–Alder reaction through η^6 -binding to ruthenium in $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$ has been achieved. Nucleophilic addition solely took place at the terminal carbon of the alkene, to give the anti-Markovnikov product. Good to excellent conversions were gained for a variety of cyclic secondary and primary amines, as well as dimethyl malonate. A Diels–Alder reaction with 1,2,3,4,5-pentamethylcyclopentadiene was achieved with moderate to good conversions. An $\text{S}_{\text{N}}\text{Ar}$ reaction with amines and dimethyl malonate has also been shown to occur with activated 4-chlorotoluene, through $[\text{RuCp}(\eta^6\text{-4-chlorotoluene})]\text{PF}_6$. Arene exchange has been achieved for $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$ with 4-chlorotoluene in up to a 69% conversion using a combination of heat and irradiation using a 400 W medium pressure mercury lamp. Unfortunately attempts to achieve a catalytic reaction proved unsuccessful.

The *N,N'*-dimethylurea promoted activation of 1-chloro-4-nitrobenzene towards $\text{S}_{\text{N}}\text{Ar}$ reactions was achieved. Under optimised conditions, good to excellent yields were obtained for a series of cyclic secondary amines. Primary and acyclic secondary amines were less successful under optimised condition, with the exception of 5-amino-1-pentanol.

The imidazole catalysed conversion of unactivated carboxylic acids to primary amides was achieved using urea as the nitrogen source. Good to excellent yield were obtained for variety of carboxylic acids under optimised conditions. It was demonstrated secondary amides could also be synthesised, when substituted ureas were used such as *N,N'*-dimethylurea and 1,3-diphenylurea, to give *N*-methyl and *N*-phenyl amides. Although possible mechanisms were explored, results so far are inconclusive.

1 Introduction: Arene activation

Due to the presence of arenes in many useful molecules in industry, in areas such as pharmaceuticals and agrochemicals, the ability to synthesise substituted arenes has been an area of interest for several decades. This has led to the development of many different synthetic techniques involving substitution reactions on arenes.

1.1 Nucleophilic aromatic substitution S_NAr

S_NAr reactions usually take advantage of the electron withdrawing ability of some functional groups, such as nitro groups (NO_2), to activate an arene. By decreasing the electron density on the ring, it becomes more susceptible to attack by a nucleophile. The increase in reactivity can lead to the substitution of a leaving group (eg. a halide) with a nucleophile to give an arene carrying a new functionality (**Figure 1.1**). The rate determining step of the reaction is the addition step. The halide used as the leaving group can have a large impact on the rate of reaction, and follows $Br < Cl < F$. The reactivity follows the order of electronegativity of the halides, as the C-X bond is polar with the carbon δ^+ , the greater the electronegativity of the halide the more δ^+ the carbon is and the more susceptible to nucleophilic attack. The electron withdrawing group has the most effect when in the *ortho* or *para* position to the halide, due to electronic effects as shown in **Figure 1.1**.

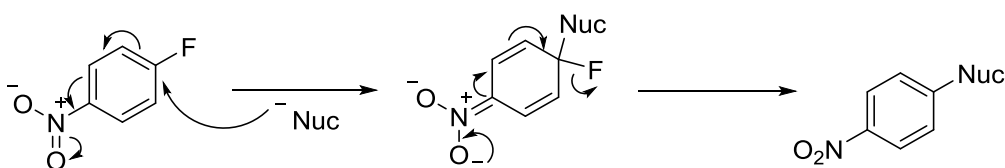


Figure 1.1: S_NAr Reaction

1.2 Electrophilic aromatic substitution S_EAr

S_EAr reactions involve the substitution of a proton on an aromatic ring with an electrophile. As above, the substituents on the ring have a directing effect on the reaction, as well as an effect on the rate of reaction. Electron donating groups are activating groups in S_EAr reactions as they increase the electron density on the ring and as demonstrated through resonance structures, are *ortho/para* directing

(**Figure 1.2**). Electron withdrawing groups are deactivating groups as the electron density on the ring is reduced.

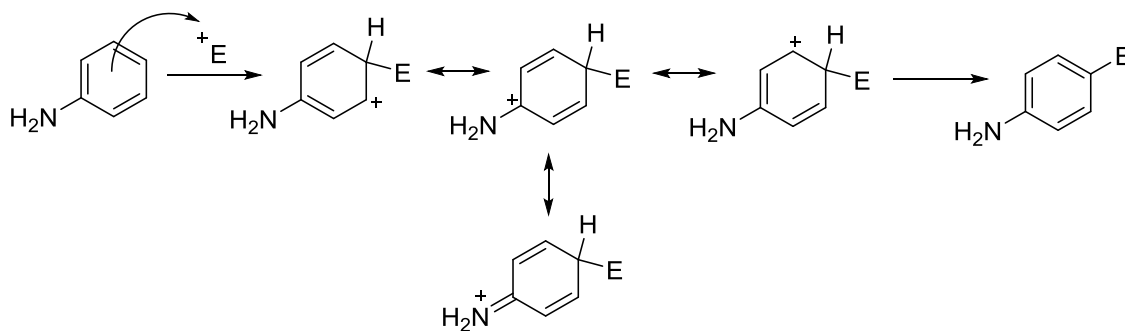


Figure 1.2: $\text{S}_{\text{E}}\text{Ar}$ reaction

1.3 Transition metal catalysed coupling reactions

Transition metal catalysed coupling reactions can be split into two categories of reaction, C-X bond activation and C-H bond activation.

1.3.1 C-X activation

A well-known category of C-X activation is the Buchwald-Hartwig amination. In 1994 the Buchwald group and the Hartwig group independently published work regarding the palladium catalysed cross coupling reaction between a halogenated arene and an amine (**Figure 1.3**).^{1,2} The palladium catalyst inserts into the Ar-X bond, followed by the cross-coupling with an amine to give the product. Both groups used Bu_3SnNR_2 to introduce the amine into the reaction and $[(o\text{-MeC}_6\text{H}_4)_3\text{P}]_2\text{PdCl}_2$ as the catalyst with Hartwig also demonstrating the use of the bromine analogue of the catalyst. Similar reaction conditions and yields were demonstrated by both groups.

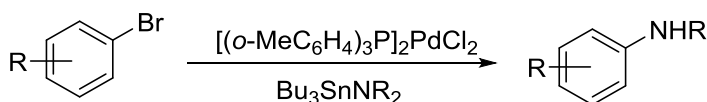


Figure 1.3: Buchwald-Hartwig amination

Due to its application within the synthetic chemistry industry, this reaction has received much attention, with many new generations of catalyst and improvements to the reaction parameters to broaden the scope. Both groups have furthered this initial work by improving the scope and reaction conditions through investigation of more efficient ligands.³⁻⁵

Xie *et al.* reported that aryl tosylates offer an attractive alternative to aryl halides as they are easily prepared from cheap and readily available starting materials and easy to handle. The optimised reaction conditions used $\text{Pd}(\text{OAc})_2$ as precatalyst, the MOP-type ligand (**Figure 1.4**), $\text{PhB}(\text{OH})_2$ as an additive and K_3PO_4 in butanol at 110°C for 15 hours. Moderate to excellent yields of 54-96% were obtained for a variety of aryl tosylates and primary amines.⁶

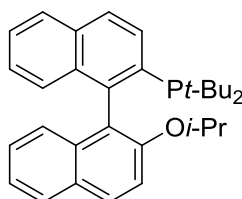


Figure 1.4: MOP-type ligand

Tardiff and others developed a chemoselective Pd system. Two phenylene *P,N*-ligands, Mor-DalPhos (L1) and *p*-Mor-DalPhos (L2) (**Figure 1.5**) with $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ as precatalyst, were used to investigate the selectivity of the system with different amines.

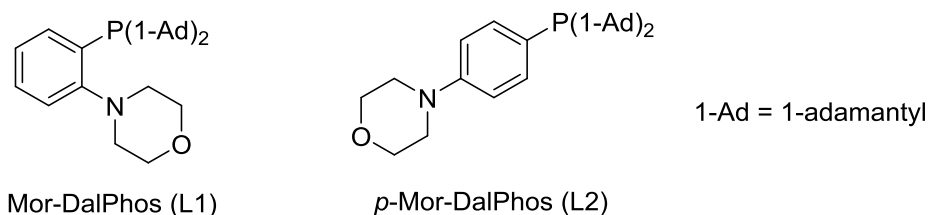


Figure 1.5: Phenylene *P,N*-ligands

The selectivity was tested using competition experiments, these involved reacting 4-chlorotoluene with aniline and a series of amines in the presence of $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ and either L1 or L2 (**Figure 1.6**), the product ratios of **1.1** and **1.2** were then used to determine selectivity. L1 was found to be highly selective, whereas L2 was not as selective, suggesting the *ortho* position on the N-group to the P-group is key to the selective nature of the ligand.⁷

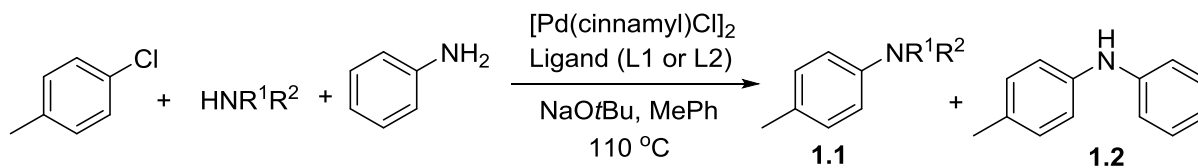


Figure 1.6: Amine arylation competition studies

Other metals have also been explored, Ackerman *et al.* investigated the amination of aryl imidazolylsulfonates and sulfamates catalysed with a nickel complex. Using $\text{Ni}(\text{cod})_2$ as a precatalyst, a series of ligand and bases were screened. Good to excellent yields were obtained with dppf as ligand and NaOt-Bu as base in toluene at 105 °C (**Figure 1.7**). It was demonstrated that the reaction conditions could be used with a number of different sulfamates and primary and secondary amines.⁸

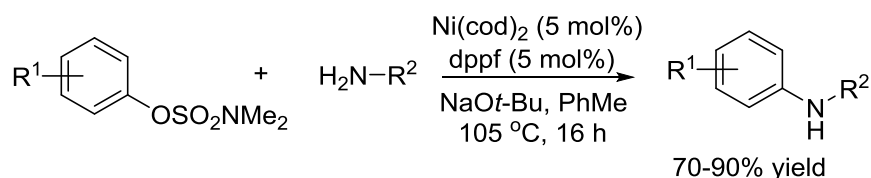


Figure 1.7: Nickel-catalysed amination of sulfamates

The Chan–Lam coupling was first reported in 1998 by Chan *et al.* and is a coupling between a phenylboronic acid and a nucleophile, usually promoted by a stoichiometric amount of copper acetate (**Figure 1.8**). The reaction involves the coordination of the XH species to the copper, followed by transmetalation of the aryl from the boron to the copper, formation of the product is achieved by reductive elimination from the copper. The reaction was shown to tolerate a wide scope of nitrogen containing nucleophile including amines, amides and sulphonamides, along with several alcohols. Various small functional groups were tolerated on the *para*-position of the boronic acid with yields varying from 4% to 96%.⁹

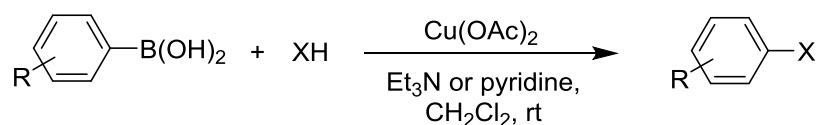


Figure 1.8: Chan-Lam coupling

As with the Buchwald–Hartwig amination, since its initial report the Chan–Lam coupling has also received much attention, with many examples of the reaction being carried out stoichiometrically and more recently catalytically.

In 2013 Srivastava and others reported the copper catalysed formation of formanilides from arylboronic acids (**Figure 1.9**). Yields of 75% to 92% were obtained for arylboronic acids with electron withdrawing and donating groups in the *ortho*, *meta* and *para* positions.¹⁰

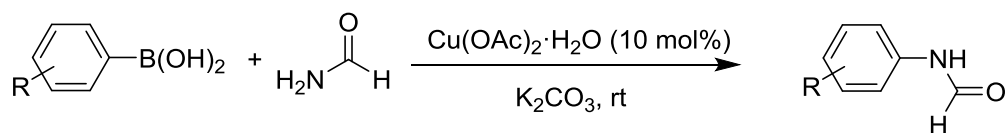


Figure 1.9: Formanilides from arylboronic acid

Other metals have also been investigated, such as the use of nickel reported by Raghuvanshi *et al.* (**Figure 1.10**). A wide variety of nitrogen containing nucleophiles, including electron poor and rich aniline, primary and secondary amines and amides gave moderate to excellent yields. Methyl and trifluoromethyl groups were also well tolerated in all positions on the arylboronic acid.¹¹

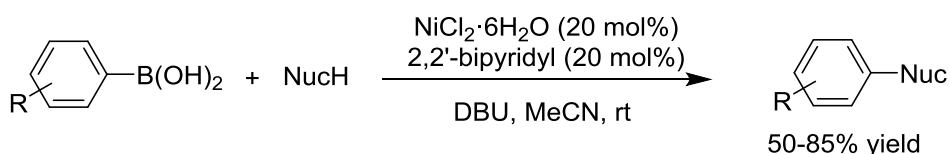


Figure 1.10: Nickel catalysed Chan-Lam

The Ullmann type reaction is a convenient copper catalysed method to couple aryls with amines and amides.¹² Similar to the Chan-Lam, the Ullmann type reaction involves the coordination of the amine/amide to a copper complex and the oxidative addition of the aryl halide (although the order of these is disputed), followed by the reductive elimination of the product.¹³

In 2009, Xi and others published a catalytic system for coupling arylhalides and N-containing heterocycles. A series of ligands and copper salts was screened to determine the optimum combinations, the conditions in **Figure 1.11** were found to give the best yields. The conditions were demonstrated to tolerate a wide variety of functionalised arylhalides, bearing both electron withdrawing and donating functionalities. A varied scope of functionalised imidazoles along with indole, pyrrole, pyrazole, and perimidine also performed well, with good to excellent yields obtained in most cases (65-99%).¹⁴

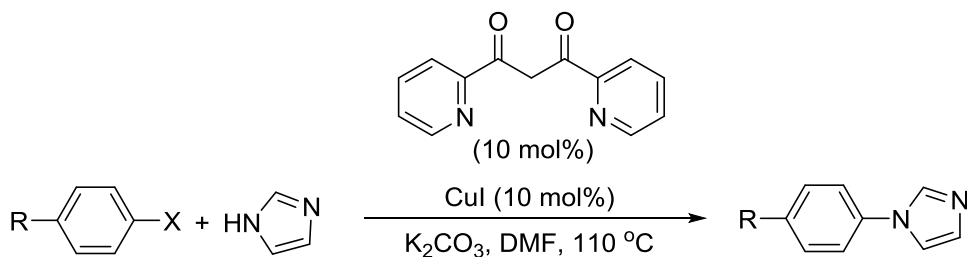


Figure 1.11: C-H coupling of aryl halides and N-heterocycles

Nui and others reported the Ullmann type coupling between arylhalides and phenols or alcohols (**Figure 1.12**). The reaction was shown to work well with both aryl bromides and iodides with electron withdrawing and donating groups present, as well as a pyridine analogue, when reacted with phenol. Phenols with methyl substituents as well as aliphatic alcohols also performed well.¹⁵

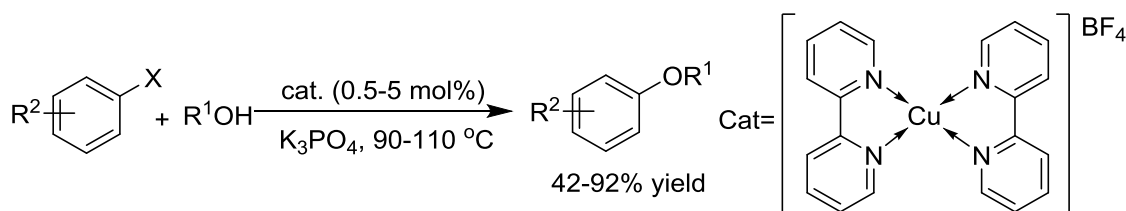


Figure 1.12: Ullmann type C-O bond formation

There are many more examples of cross-coupling reactions in the literature, including C-C cross coupling, such as, the Suzuki-Miyaura coupling, the Sonogashira coupling and the Heck reaction. More information on these and other cross-coupling reactions can be found in recent reviews.^{13,16-20}

1.3.2 C-H activation

Murai *et al.* reported activation of the C-H bond in the *ortho* position to an aromatic ketone, catalysed by $\text{RuH}_2(\text{CO})(\text{P}(\text{C}_6\text{H}_5)_3)_3$, resulting in a coupling between the aromatic ring and an olefin (**Figure 1.13**). The reaction conditions were shown to give quantitative yields for a variety of substituted keto-arenes and small olefins. It was proposed that coordination of the carbonyl group brought the *ortho* C-H closer to the Ru, resulting in cleavage of the C-H bond and cyclometallation. Olefin insertions of the Ru-H bond followed by reductive elimination yields the product.²¹

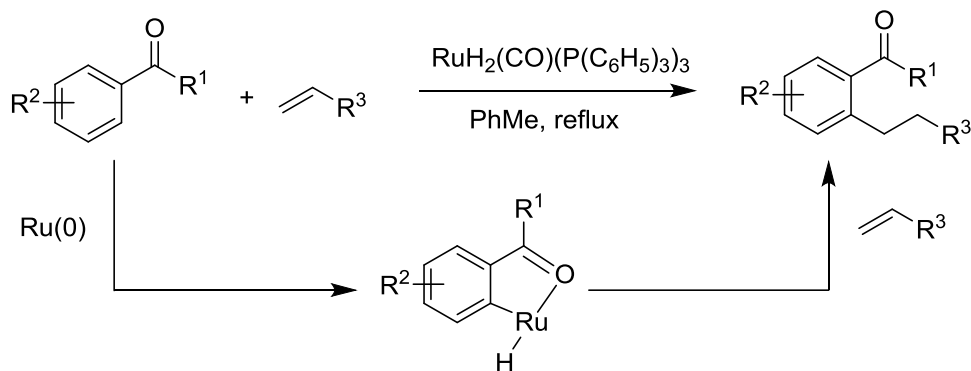


Figure 1.13: C-H activation of keto-arenes

Dick, Hull and Sanford reported the palladium catalysed activation of benzo[*h*]quinoline, as this was known to undergo cyclopalladation (**Figure 1.14**). The nitrogen acts as a directing group for C-H activation in the γ -position. Using different small alcohols as the solvent and an oxidant, afforded a series of ether products, alternatively halogenating agents (NCS/NBS) in acetonitrile gave the corresponding halogenated product all in good to excellent yields (71-95%). Substitutions were also shown to take place with a variety of aryl substrates with an available hydrogen in the γ -position to an sp^2 nitrogen.²²

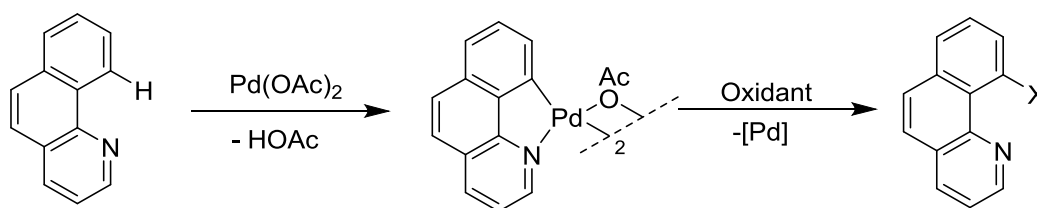


Figure 1.14: Pd(II)-catalysed oxidation of benzo[*h*]quinoline

Sanford and others furthered the research through the introduction of a directing group (X) on the aryl ring. As the aryl groups are joined by a bond with free rotation, the introduction of an FG leads to a selective reaction, as the functional group blocks one of the possible reaction sites. In all examples, the reaction shows selectivity towards product **1.3** (**Figure 1.15**). When X is a small substituent such as F the selectivity was only 6:1, but for larger groups the selectivity ranges from 20:1 up to 60:1 for a methyl ether group.²³

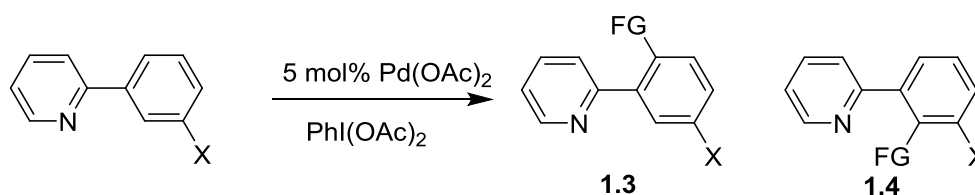


Figure 1.15: Selective functionalisation

Again using $Pd(OAc)_2$ the same group demonstrated the acetoxylation and etherification of arenes using oxone as the oxidant (**Figure 1.16**).²⁴

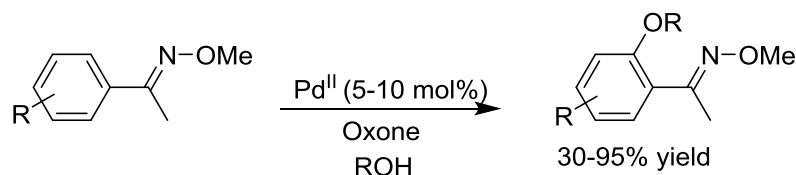


Figure 1.16: C-H bond oxygenation with oxone

Yang *et al.* demonstrated the *ortho*-arylation of an sp^2 C-H bond catalysed by palladium (**Figure 1.17**). The reaction tolerated the introduction of a series of *meta* and *para* substituted arenes, along with substituents in the *meta* and *para* position of the phenyl ring in the starting material (**1.5**), with moderate to very good yields (25-95%). The reaction conditions were also shown to catalyse the *ortho*-arylation of acetylated anilines.²⁵

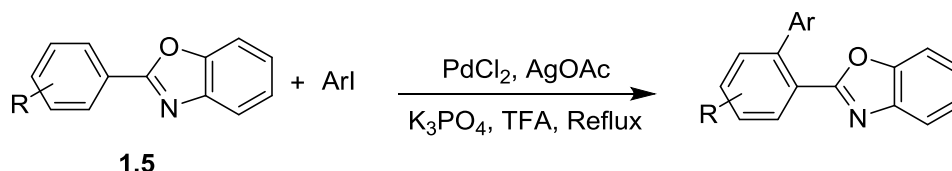


Figure 1.17: *Ortho*-arylation of sp^2 C-H bond

More extensive reviews of C-H activation can be found in the literature.^{26,27}

1.4 Activation by η^6 binding to metal

Another method of activation is to bind the π system of a non-activated arene, η^6 to a metal centre, this withdraws electron density from the ring activating it to attack by nucleophiles (**Figure 1.18**). A number of different metals can be used, these including chromium,²⁸ rhodium,²⁹ iron³⁰ and ruthenium.³¹

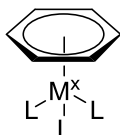


Figure 1.18: η^6 -Bound arene-metal complex

Although this method is valuable in the activation of arenes, there are drawbacks. When the metal centre is positively charged, the arene is activated to nucleophilic attack due to the reduction of electron density on the ring. Due to this strong interaction, exchange of one arene for a different arene can be difficult. Alternatively, if the metal is not charged, the arene is less activated to attack by a nucleophile. As the reduction of electron density is not as great as when the metal is charged, exchange of the arene is earlier as the interaction between the metal and the ring is weaker.

In 2010 Otsuka *et al.* published the first example of a catalytic S_NAr reaction between a non-activated arene and an amine. After investigating several ruthenium

and rhodium complexes it was found that a Ru catalyst prepared from Ru(cod)(2-methylallyl)₂ (5 mol%), DPPent (7 mol%) and trifluoromethanesulfonic acid (10 mol%) gave the highest activity. Optimised conditions used the catalyst system shown in **Figure 1.19**, with Et₃SiH (1 equivalent) and Et₃N (1 equivalent) as additives in dioxane at reflux. The reaction was shown to work with a range of fluoroarenes and amines, and moderate to good yields of up to 79% were obtained.³²

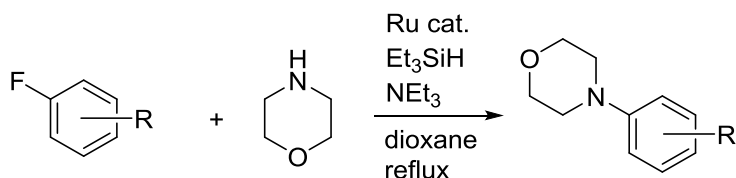


Figure 1.19: Ru-catalysed S_NAr reaction

This work was further developed to find a more stable catalyst precursor, [Ru(benzene)Cl₂]₂ was chosen. After screening reaction conditions it was found that [Ru(benzene)Cl₂]₂ (2.5 mol%), silver triflate (10.5 mol%), P(*p*-FC₆H₄)₃ (12 mol%), with 4 Å molecular sieves in dioxane at reflux were optimal. The scope of the reaction was examined with a range of fluoroarenes with morpholine, moderate to good yields were obtained. It should be noted that this reaction only works well with fluoroarenes, other haloarenes do not work well under these conditions. The key reaction intermediates were isolated, **Figure 1.20** shows the complex which is thought to react with morpholine in the S_NAr reaction. The rate determining step in this reaction is the arene exchange, with the addition of the nucleophile taking place relatively fast. This contrasts with a standard S_NAr reaction where the addition of the nucleophile is the rate determining step.³³

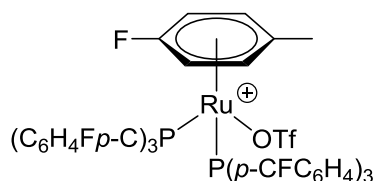


Figure 1.20: Key reaction intermediate

Takaya and Hartwig carried out a mechanistic study into the anti-Markovnikov hydroamination of vinylarenes through η^6 -binding to ruthenium. The nucleophilic addition took place readily with 20 equivalents of morpholine at 20-50 °C in dioxane and *N*-methyl-2-pyrrolidone (NMP) and the arene exchange was found to take place with 40 equivalents of styrene at 100 °C in a mixture of NMP and dioxane. The

catalytic cycle shown in **Figure 1.21** is the proposed mechanism and is consistent with the mechanistic data.³⁴

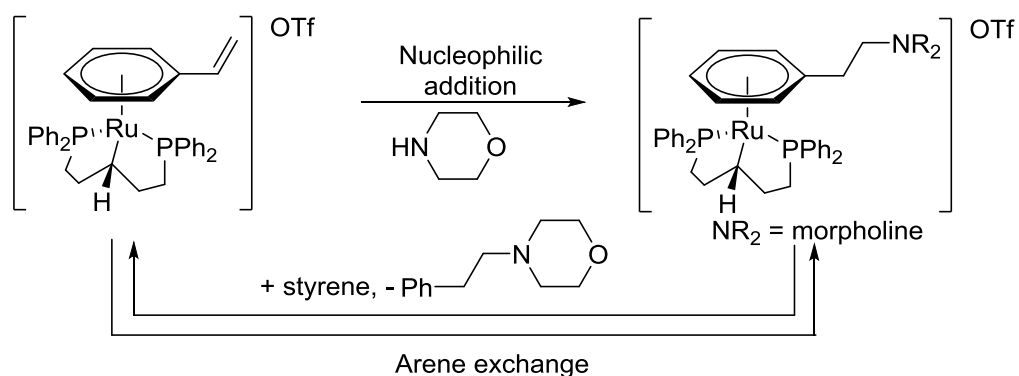


Figure 1.21: Catalytic cycle

This is just a brief overview of the extensive number of articles in the literature that cover many different modes of arene activation. A more detailed review of arenes activated through being bound η^6 to a metal and through the presence of an electron withdrawing group will be given in Chapter 3.

2 Introduction: Organocatalysis

Metal catalysis has been widely used for the promotion of organic reactions. Although metal catalysis offers a huge versatility of transformations which can be achieved, there are disadvantages to using metal catalysts. They can be expensive due to the use of rare metals and complicated ligands, as well as toxic and sensitive to air and moisture. For this reason in the past decade and a half organocatalysis has become an ever growing field, with the number of publications increasing from a couple of papers a year before 2000 to more than 600 publications in 2008.³⁵ Organocatalysts offer an attractive alternative to metals as they are often less expensive with simpler examples being inexpensive. They are generally less toxic and are normally not air and moisture sensitive, meaning special reaction environments are not needed, again reducing the cost. Many examples can be taken from nature, which means they are available in enantiomerically pure form, such as proline.

Organocatalysis can be categorised into several modes of activation, these include H-bonding catalysis, either through single or double H-bonds donors, formation of enamines or iminiums, and ammonium salts, along with other examples. These categories have been shown to catalyse a wide variety of reactions.

2.1 Urea and thiourea catalysis

One of the first examples of the use of ureas and thioureas as catalysts was reported by Sigman and Jacobsen in 1998 in an enantioselective Strecker reaction. They report the use of ureas and thioureas containing Schiff bases. A library of Schiff base ureas and thioureas was screened and it was found that the thiourea shown in **Figure 2.1** gave the greatest enantioselectivity.³⁶ Further mechanistic investigation was carried out by the same group. NMR studies and structural analysis suggested that the imine forms H-bonds with both the hydrogens in the thiourea, with the functional group on the imine pointing into the solvent away from the bulky groups of the catalyst, leading to the highly selective hydrocyanation of the imine.³⁷

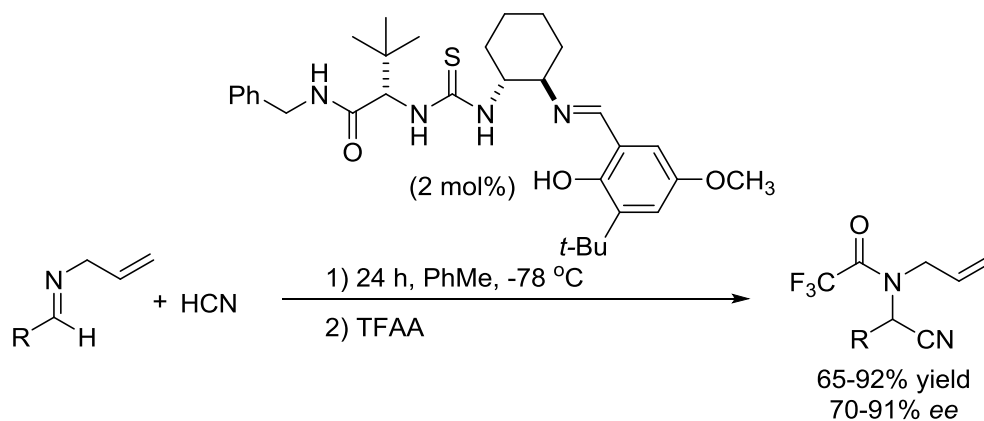


Figure 2.1: Schiff base catalysed Strecker reaction

There are many more examples of ureas and thiourea catalysis and these will be covered at the start of Chapter 4.

2.2 Diol catalysis

Diols have also been shown to act as catalysts through hydrogen bond donations. An early example of this was an epoxide aminolysis catalysed by 1,8-biphenylenediol reported by Hine *et al.* (**Figure 2.2**). It is proposed that double hydrogen bonds form from the diol to the epoxide oxygen, making the carbon more susceptible to attack by the amine.³⁸

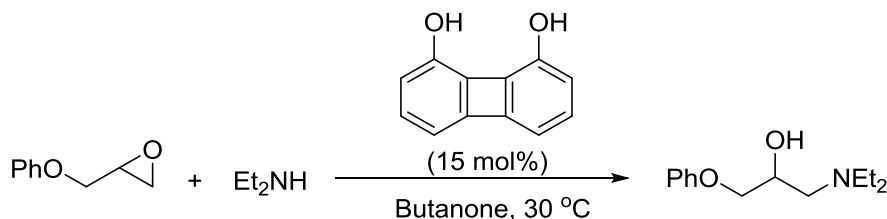


Figure 2.2: Aminolysis of an epoxide

McDougal and others reported a Morita-Baylis-Hillman reaction catalysed by a BINOL derivative. Various BINOL derivatives were screened, it was found those with bulky phenyl groups ortho to the hydroxyl group gave the best conversion and enantioselectivity (**Figure 2.3**). Under optimised conditions, a series of aldehydes was shown to give moderate to good yields (39-88%) and enantioselectivity (67-96%).³⁹

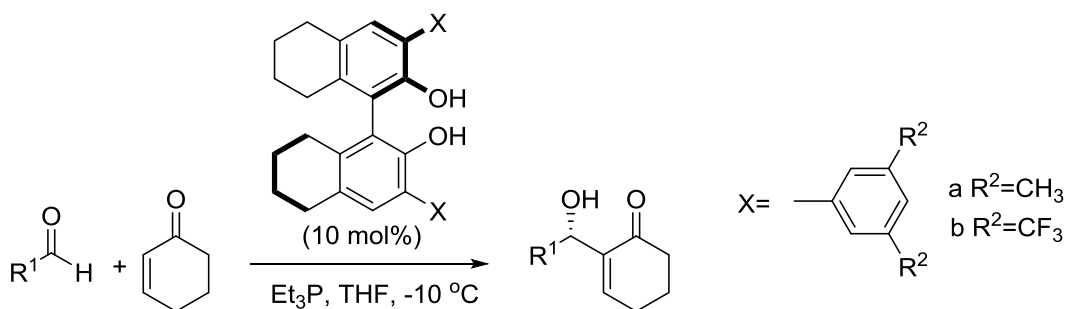


Figure 2.3: Diol catalysed Morita-Baylis-Hillman reaction

An aza-Morita-Baylis-Hillman reaction catalysed by a BINOL analogue (**Figure 2.4**) was reported by Matsui and others. Similar to the Morita-Baylis-Hillman reaction, an imine is used instead of an aldehyde. Excellent yields of 88-99% and enantioselectivities of 88-95% were achieved for a series of aryl imines and small α,β -unsaturated carbonyls.⁴⁰

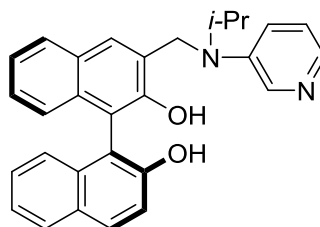


Figure 2.4: Diol used in aza-Morita-Baylis-Hillman reaction

Rawal and co-workers reported the hetero-Diels-Alder reaction between unactivated aldehydes and 1-amino-3-siloxydiene catalysed by the diol, TADDOL ($\alpha,\alpha',\alpha',\alpha'$ -tetraaryl-1,3-dioxolan-4,5-dimethanol) (**Figure 2.5**).⁴¹

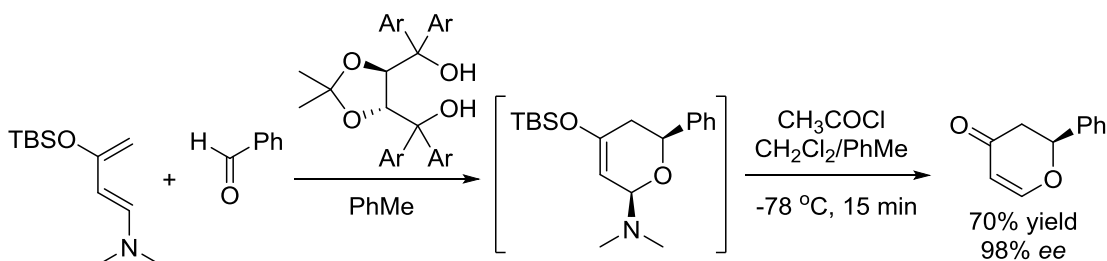


Figure 2.5: Hetero-Diels-Alder catalysed by TADDOL

2.3 Proline catalysis

Proline has been shown to catalyse a wide variety of reactions. Its normal mode of activation is through forming a covalent bond with the reaction substrate to go through an iminium or enamine intermediate.

An early example of proline catalysis was the intramolecular aldol reaction reported by Eder and others in 1971 (**Figure 2.6**). It was noted that the configuration of the product reflected the configuration of the proline used, with the (*S*)-enantiomer of the catalyst leading to the (*S*)-enantiomer of the product.⁴²

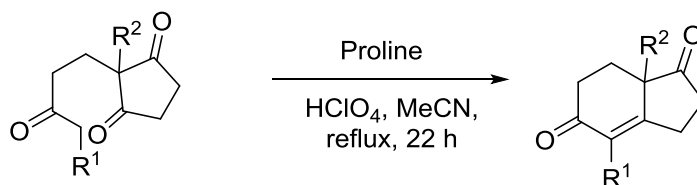


Figure 2.6: Intramolecular aldol reaction

MacMillan *et al.* reported the direct and enantioselective aldol reaction between two different aldehydes (**Figure 2.7**). Good yields of up to 88% and excellent enantioselectivities of 97 to >99% were obtained with methyl or *n*-butyl groups in the R^1 position and various groups in the R^2 position. A decrease in enantioselectivity to 91% was observed with a benzyl group in the R^1 position.⁴³

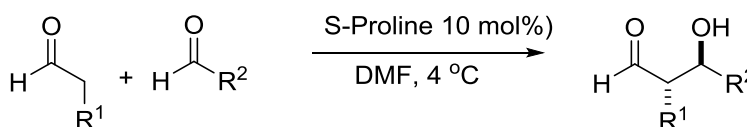


Figure 2.7: Direct enantioselective cross-Aldol

There are also many examples of aldol reactions catalysed by proline analogues. For example Yu and others reported the asymmetric aldol reaction catalysed by 4,5-methano-L-proline.^{44,45} The synthesis of chiral biaryls through atroposelective aldol condensation was reported by Link and Sparr.⁴⁶

More recently Martínez-Castañeda and others reported the diastereoselective aldol reaction catalysed by proline and co-catalysed by a guanidinium salt. Each of the four possible diastereomers of the aldol reaction were accessed using a different combination of catalyst and cocatalyst (**Figure 2.8**). The BF_4^- guanidinium salt **2.1** yielded the anti-diastereomers and the BPh_4^- guanidinium salt (**2.2**) yielded the syn-diastereomer. In each case the (*R*)-proline gave the *S* enantiomer of the alcohol and (*S*)-proline gave the *R* enantiomer of the alcohol.⁴⁷

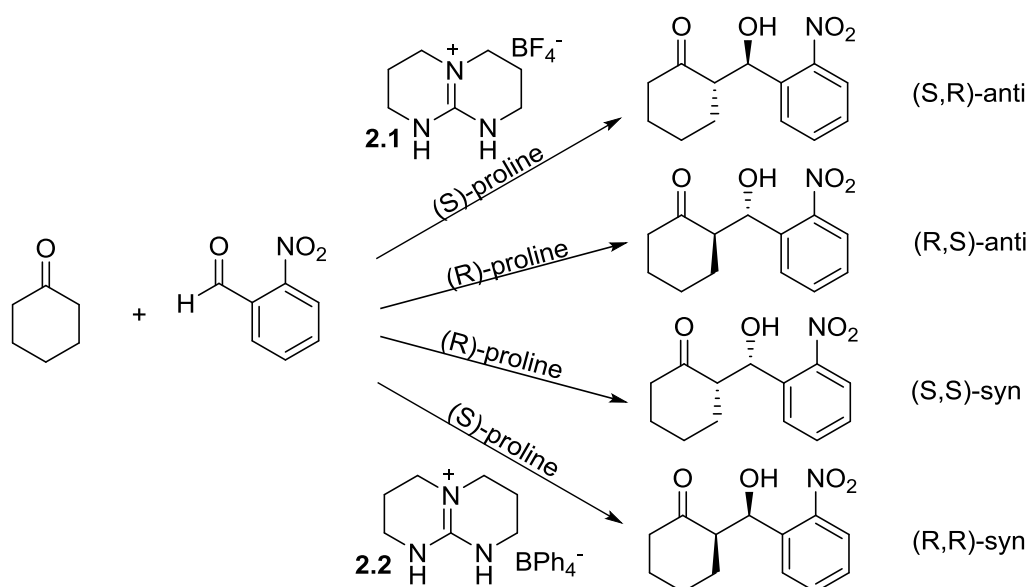
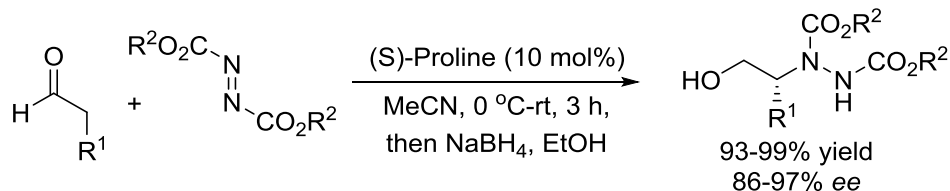
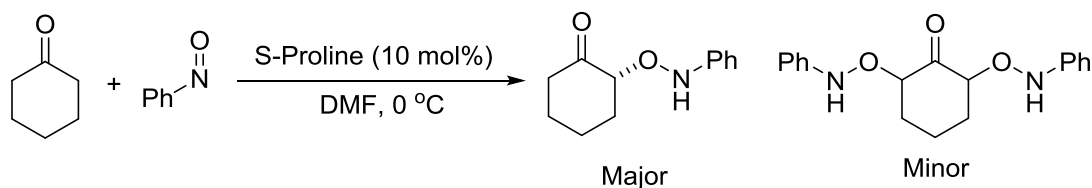


Figure 2.8: Diastereoselective aldol reaction

List reported the direct α -amination of aldehydes with azodicarboxylates, catalysed by proline (**Figure 2.9**). Excellent yields and enantioselectivities were obtained for alkyl and benzyl groups in both the R^1 and R^2 positions. It was also noted that the product could be further reacted to produce 2-oxazolidinones.⁴⁸

Figure 2.9: α -Amination of aldehydes

The proline catalysed direct α -aminooxylation of ketones with nitroso compounds was reported by Hayashi and co-workers (**Figure 2.10**). The reaction was selective for O-arylation, although double addition does take place to give the α,α' -diaminoxylation as a minor product. A series of symmetric cyclic ketones gave yields of 40 to 96% and enantioselectivities of $>99\%$ in most cases.⁴⁹

Figure 2.10: α -aminooxylation of aldehydes and ketones

Chacko and Ramapanicker have recently demonstrated how the α -aminoxylation of aldehydes can be used in the synthesis of polyhydroxypiperidines (**Figure 2.11**). Treatment with copper acetate removes the -NHPh , yielding the alcohol. The method was demonstrated to be valuable in creating stereocentres which could be carried through the whole synthesis.⁵⁰

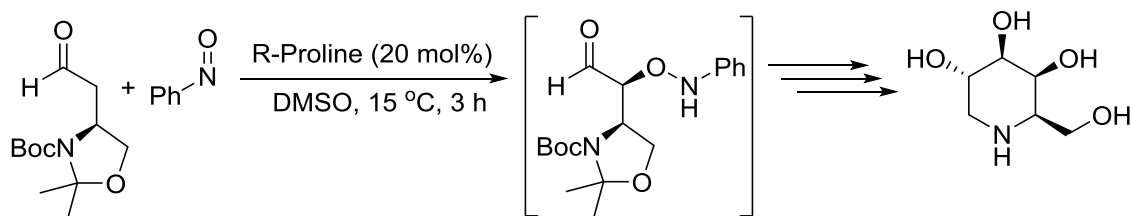


Figure 2.11: Proline catalysed α -aminoxylation of aldehydes in the synthesis of polyhydroxypiperidines

The first proline analogue catalysed hetero-Diels–Alder reaction (**Figure 2.12**) was reported by Juhl and Jørgensen in 2003. Aliphatic and aromatic groups were tolerated in the R^1 and R^2 positions and small alkyl groups at R^3 . Good to very good enantioselectivities (80-94%) were achieved for a series of substrates with moderate to good yields (65-93%).⁵¹

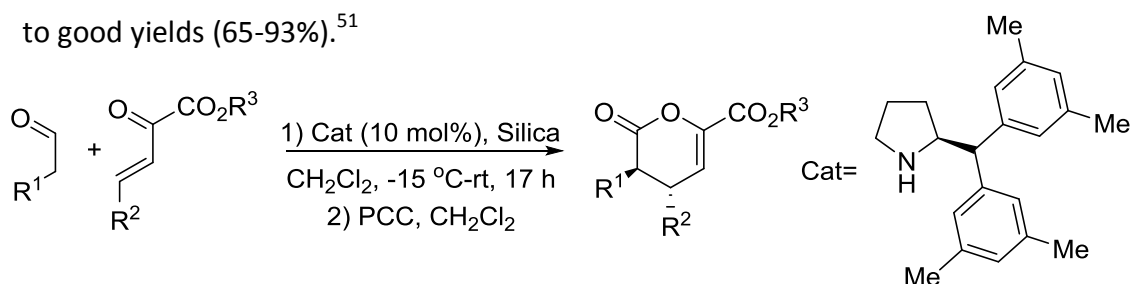


Figure 2.12: Proline analogue catalysed hetero-Diels–Alder

The three-component one-pot aza-Diels–Alder reaction was reported by Rajanardar and co-workers (**Figure 2.13**). The reaction between an aniline or aminoisoxazole, an aryl aldehyde and a nitrostyrylisoxazole yields either isoxazolyl tetrahydroquinolines or isoxazolo[2,3- α]pyrimidines (**2.5** and **2.6**). Yields of between 82% and 90% were obtained for *para* substituted aryls for both Ar^1 and Ar^2 . The trans-isomer **2.5** was the major product over the cis-isomer **2.6** in all examples reported.⁵²

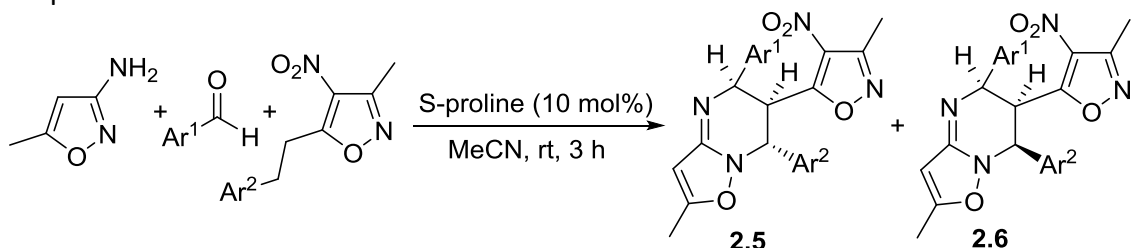


Figure 2.13: Three-component one-pot aza-Diels–Alder

A three-component, one-pot, cross-Mannich S-proline catalysed reaction (**Figure 2.14**) was reported by Hayashi and others. The direct and enantioselective reaction was shown to tolerate several aryl aldehydes in very good yields and diastereoselectivities. Although a yield of 90% was achieved when R² was methyl a significant decrease in conversion was seen when longer alkyl chains were used with a yield of only 55% for n-propyl.⁵³

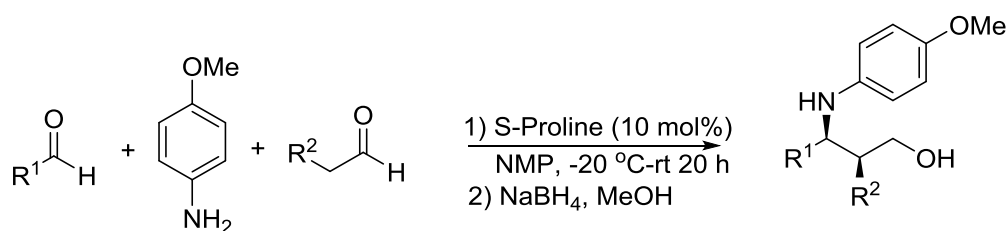


Figure 2.14: Three-component one-pot cross Mannich reaction

The proline analogue, 3-methyl-β-proline, was demonstrated to catalyse an enantioselective anti-Mannich type reaction between glyoxylate imine and a series of aldehydes and ketones (**Figure 2.15**), was reported by Nagata *et al.* The reaction was shown to work for a series of aldehydes and cyclic ketones with low catalytic loadings, a higher catalyst loading was needed for acyclic ketones. The β-proline analogue was shown to outperform unsubstituted β-proline as a catalyst for all examples shown, although in some cases better diastereoselectivities were achieved when unsubstituted β-proline was used.⁵⁴

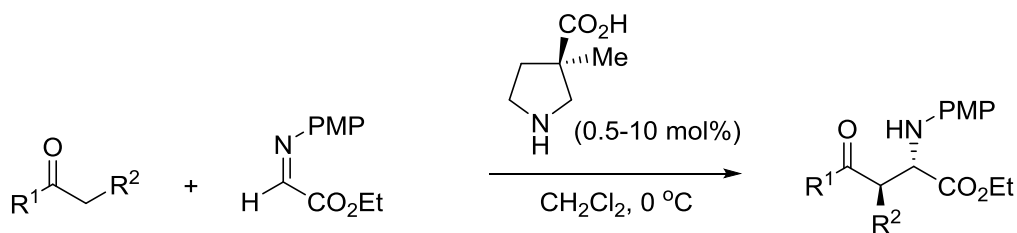


Figure 2.15: 3-Methyl-β-proline catalysed anti-Mannich type reaction

Chacko and Ramapanicker reported the S-proline catalysed one-pot, three-component Mannich reaction as a method of synthesising 2-substituted piperidine and pyrrolidines (**Figure 2.16**). Both the functionalised piperidine and pyrrolidine were gained in very good yields, although triethylamine was also needed in the piperidine case to gain a good yield. It was shown that the piperidine product could easily be transformed in 2 steps into several alkaloids.⁵⁵

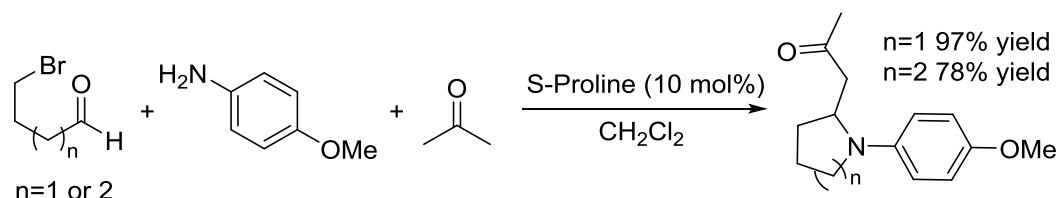


Figure 2.16: S-Proline one-pot, three-component Mannich reaction

Although proline has been shown to be a successful catalyst for many reactions, one reaction with which little success has been had was the Michael addition. Although attempts have been made with both proline and proline analogues, low yields and poor enantioselectivities are often achieved.⁵⁶ For this reason computational studies have been carried out to understand the nature of the mechanism further, this is not covered in the scope of this report but more information can be found in the literature.^{57,58}

2.4 Imidazolidinone catalysis

In 2001 Paras and MacMillan reported the organocatalyzed Friedel–Crafts alkylation of pyrroles by α,β -unsaturated aldehydes (**Figure 2.17**). The organocatalyst used was a functionalised imidazolidinone. *N*-Methylpyrrole was shown to react well with aliphatic and aromatic α,β -unsaturated aldehydes, with good to excellent yields and very good enantioselectivities. It was demonstrated that cinnamaldehyde reacted with pyrroles with various functionality on the nitrogen as well as groups in the 2 and 3 position.⁵⁹

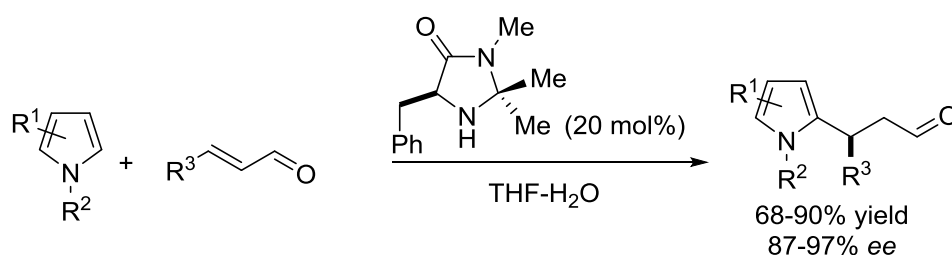


Figure 2.17: Friedel–Crafts alkylation

Brown and others reported the Mukaiyama-Michael reaction of α,β -unsaturated aldehydes with silyloxy furans (**Figure 2.18**). Aliphatic, aromatic and ester groups were well tolerated in the R^1 position, as well as small alkyl and ester groups in the R^2 position. Excellent enantioselectivity (up to 99%) was achieved and the syn:anti ratios varied from 1:6 to 31:1.⁶⁰

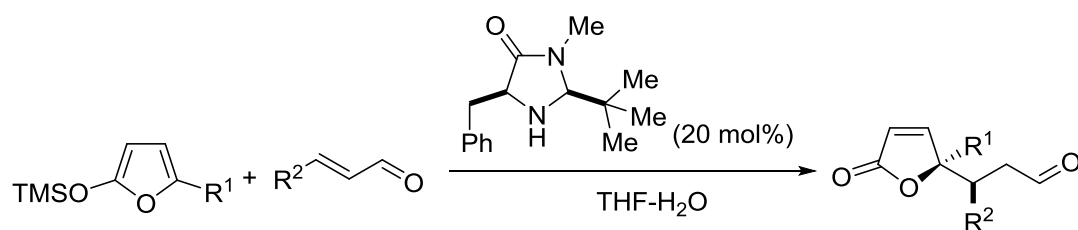


Figure 2.18: Mukaiyama-Michael reaction

The imidazolidinone catalysed benzylic C-H functionalisation was reported by Benfatti and others (**Figure 2.19**). The reaction was shown to proceed with moderate stereoselectivity (38-78% ee). In the R position larger aliphatic groups were tolerated well (50-90% yield), although aromatic groups resulted in a decrease in yields (30%). Functionalisation of benzylic indoles was also attempted with moderate yields.⁶¹

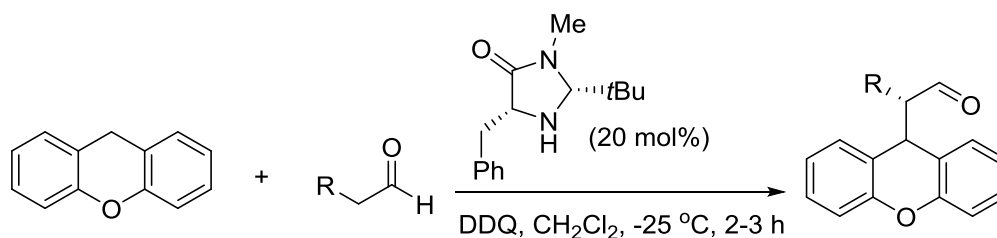


Figure 2.19: Imidazolidinone catalysed benzylic C-H functionalisation

Shen *et al.* reported an ionic liquid-supported imidazolidinone catalysed Diels-Alder reaction (**Figure 2.20**). A co-catalyst of CF_3COOH was demonstrated to optimise yields, with a solvent mixture of acetonitrile:water. Various α,β -unsaturated aldehydes gave yields of 45 to 99 %, although little to no selectivity between *endo* and *exo* product was observed, enantioselectivities of up to 94% were achieved. The recyclability of the catalyst was investigated, after 5 cycles no reduction in catalytic activity was observed.⁶²

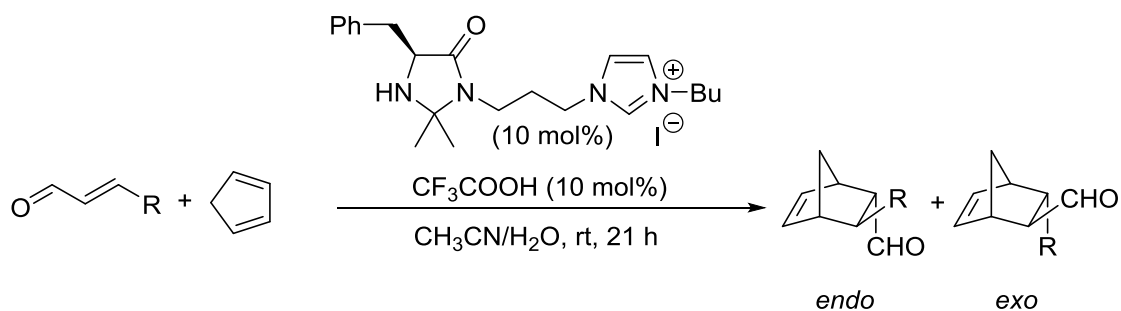


Figure 2.20: Ionic liquid-supported imidazolidinone catalysed Diels-Alder reaction

2.5 Ammonium salts catalysis

Bluet and Campagne reported the ammonium hydroxide salt catalysed Mukaiyama–Aldol reaction (**Figure 2.21**). Although initially exploring ammonium salts with a fluoride counter ion, a hydroxide analogue was found to give better results. A quantitative yield was gained for the reaction, compared with a 70% yield when the fluoride ion salt was used. Disappointingly, an *ee* of only 30% was achieved, although this was better than the figures for the fluoride salts.⁶³

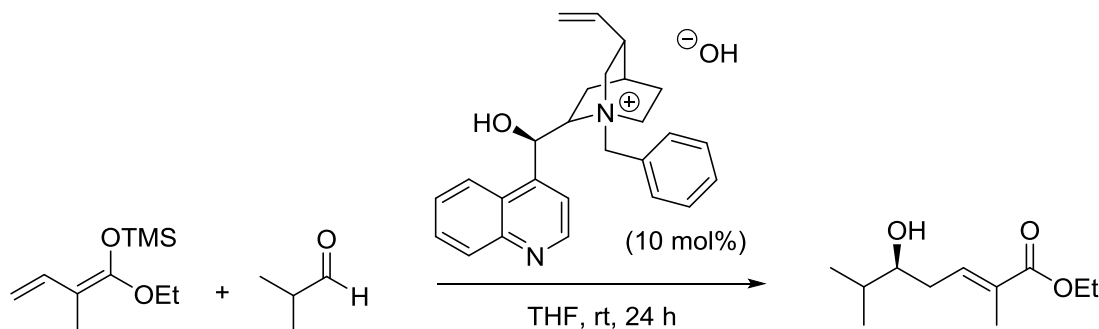


Figure 2.21: Ammonium hydroxide salt catalysed Mukaiyama–Aldol

The asymmetric nitroaldol reaction between aromatic aldehydes and silyl nitronates catalysed by a quaternary ammonium difluoride salt (**Figure 2.22**) was reported by Ooi and others. The reaction was shown to work well with a range of functionalities in the R^1 , R^2 and R^3 position, with excellent yields and enantioselectivities. Interestingly, in a reaction where R^2 is *t*-Bu, R^1 is Me and R^3 is Ph, after 2 hours a yield of 83% was obtained with an *ee* of 33%, but after 3 hours a slight increase in yield to 92% had occurred but the *ee* was now 95%. With the bulkier *tert*-BuMe₂ as R^2 a large decrease in *ee* was observed, only achieving 11 %, although Et₃ gave an *ee* of 92%.⁶⁴

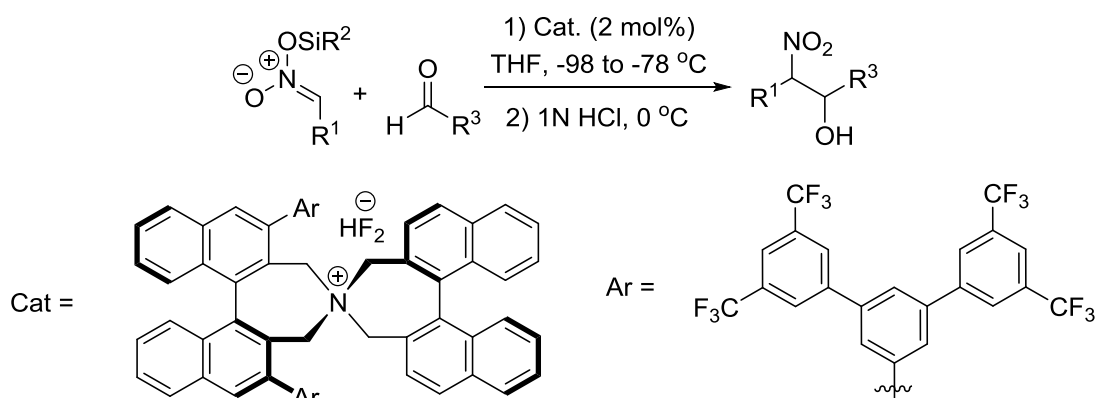


Figure 2.22: Asymmetric nitroaldol reaction

The fixation of CO₂ with epoxides to form carbonates was reported by Wang *et al.* in 2012 (**Figure 2.23**). A series of simple quaternary ammonium salts was investigated, Bu₄NBr was determined to perform the best. Moderate to good yields were obtained with R= H, Me and Ph, although as the size of the group increases the yield decreases. It is thought the reaction goes through ring opening by the salt counter ion (Br⁻), followed by incorporation of the CO₂ then cyclisation.⁶⁵

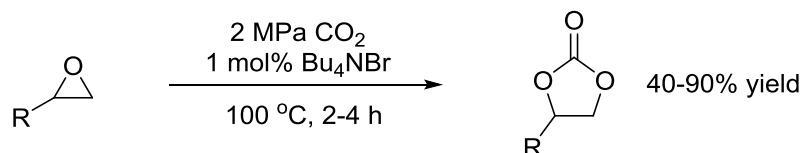


Figure 2.23: CO₂ fixation with epoxides

Shi and Glorius reported the use of the same catalyst in the synthesis of fluorenones through the intramolecular cyclisation of aldehyde containing biaryls (**Figure 2.24**). Several oxidants were screened, K₂S₂O₈ was found to give the best yield. The reaction was shown to tolerate both electron withdrawing and donating groups on Ar² in good yield, as well as halogens on Ar¹ (54-92%). Moderate yields were also gained with bulkier fused rings in the Ar² position (35-62%).⁶⁶

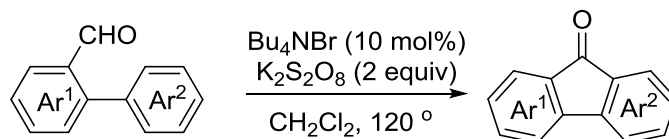


Figure 2.24: Intramolecular cyclisation of aldehyde containing biaryl

There are many more examples of organocatalysis in the literature, such as the use of guanidine and amidines,⁶⁷⁻⁷⁰ N-oxides,⁷¹⁻⁷⁴ sulfoxides⁷⁵⁻⁷⁷, carbenes⁷⁸⁻⁸⁰ and phosphorus based catalysis.^{81,82} There are also many reviews in the area.⁸³⁻⁸⁷ A more detailed report of urea catalysis will be given in Chapter 4.

**3 Activation of styrene and 4-chlorotoluene
through η^6 -binding to a ruthenium
cyclopentadienyl complex**

3.1 Introduction

3.1.1 Activation by η^6 binding to metal

As mentioned in Chapter 1, activation of arenes can be achieved through binding the π system of a non-activated arene, η^6 to a metal centre. This withdraws electron density from the ring, activating it to attack by nucleophiles (**Figure 3.1**). A number of different metals can be used, including chromium,²⁸ rhodium,²⁹ iron³⁰ and ruthenium.³¹

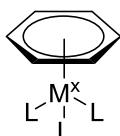


Figure 3.1: η^6 -Bound arene-metal complex

Martinez and others investigated the perallylation of arenes bound to CpFe^+ followed by alkene metathesis using Grubbs catalysts. Activation of the benzyl C-H bonds through η^6 binding to Fe, resulted in their substitution with allyl bromide. On the introduction of a Grubbs catalyst, intramolecular metathesis took place between the two allyl groups to form a 5 membered ring (**Figure 3.2**).³⁰

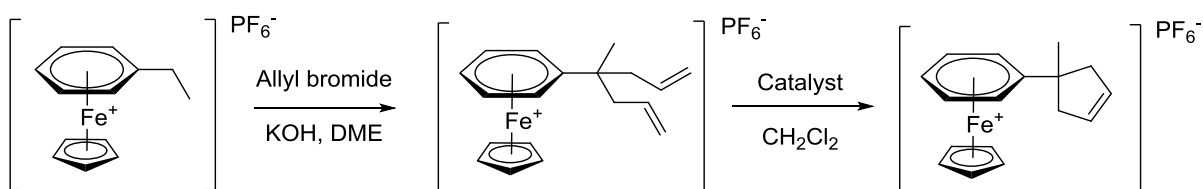


Figure 3.2: Intramolecular metathesis

The first reported synthesis of $[\text{RuCp}^*(\eta^6\text{-arene})]\text{OTf}$ from $[\text{RuCp}^*(\text{CH}_3\text{CN})_3]^+$ was by Dembek and Fagan. The activation of aryl chlorides was demonstrated using aromatic nucleophilic substitution ($\text{S}_{\text{N}}\text{Ar}$) with oxygen and sulfur nucleophiles.⁸⁸

In 1996 Cambie and others used a similar method to synthesise $[\text{RuCp}(\eta^6\text{-arene})]\text{PF}_6$ from $[\text{RuCp}(\text{CH}_3\text{CN})_3]\text{PF}_6$, it was demonstrated that a variety of functionalised arenes could be bound to the metal centre with good yields (**Figure 3.3**). $[\text{RuCp}(\text{CH}_3\text{CN})_3]\text{PF}_6$ proved to be a valuable precursor to $[\text{RuCp}(\eta^6\text{-arene})]\text{PF}_6$ sandwich complexes, due to the labile nature of the bond between acetonitrile and ruthenium. $\text{S}_{\text{N}}\text{Ar}$ reactions were demonstrated with Ru bound chlorobenzene and *o*-dichlorobenzene, and both oxygen and nitrogen nucleophiles gave good yields,

although a large excess of nucleophile was used. Cleavage of the arene from the ruthenium was achieved by irradiation of the complex in the presence of acetonitrile, to give the free arene species and $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$.⁸⁹

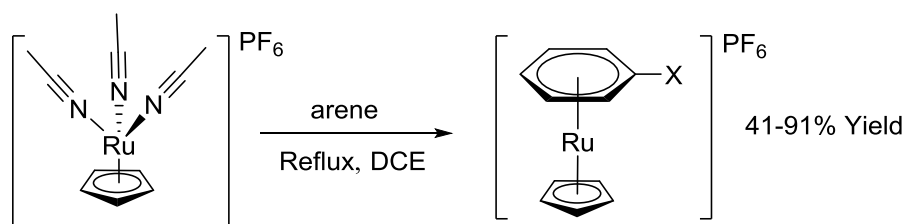


Figure 3.3: Synthesis of $[\text{RuCp}(\eta^6\text{-arene})]\text{PF}_6$

Ruiz and Astruc investigated permethylation of C_6Me_6 in the complex $[\text{FeCp}^*(\eta^6\text{-C}_6\text{Me}_6)]\text{PF}_6$ in the presence of excess base. Methylation was not selective to the 6 membered ring, also taking place on the Cp^* ring; complete methylation of the 6 membered ring did not occur. It was thought this may be due to steric constraints, and using ruthenium may solve this problem. With the change to $[\text{RuCp}^*(\eta^6\text{-C}_6\text{Me}_6)]\text{PF}_6$, the selective hexamethylation, hexaallylation and hexabenzoylation of C_6Me_6 were achieved (Figure 3.4).³¹

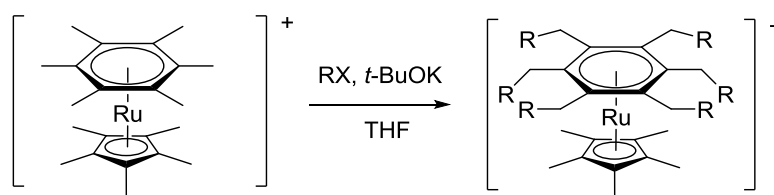


Figure 3.4: Permethylation of η^6 -bound C_6Me_6

Although these reactions provide an excellent way to activate arenes, one of the main problems is that in many cases a stoichiometric amount of metal is needed. This is not ideal, as some metals can be rare and expensive, such as ruthenium. For this reason, finding ways to carry these reactions out catalytically has become of interest.

Houghton and Voyle reported in 1984 a catalytic intramolecular cyclisation of a series of 3-(2-fluorophenyl)propanols (Figure 3.5), where the arene was activated though η^6 -binding to rhodium. The rhodium catalyst used was $[\text{Rh}(\eta^5\text{-C}_5\text{EtMe}_4)]^{2+}$ with PF_6^- or BF_4^- as the counterions.²⁹

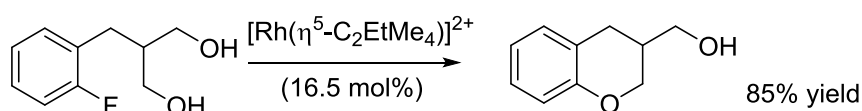


Figure 3.5: Intramolecular cyclisation

The activation of arenes by complexation to chromium, through $[\text{Cr}(\eta^6\text{-arene})(\text{CO})_2\text{L}]$ was reported by Semmelhack *et al.* The major hurdle to overcome was to achieve efficient arene exchange, by finding a ligand which could bind to the chromium centre and lower the activation barrier for the arene exchange. Ideally a chelating ligand would have a side chain which could reversibly bind to the metal centre. When bound, the ligand would allow the arene to bind η^4 to the metal, lowering the activation energy for arene exchange (**Figure 3.6**). A series of (2-L'-pyrrolyl)-(pyrrolyl)₂phosphine ligands, where L' was various coordinating groups with different steric and electronic properties were examined. Some ligands showed a significant increase in the rate of arene exchange, in some cases the exchange was observed to take place at 23 °C. It was also noted that for some ligands the rate showed a significant dependence on the properties of the incoming and outgoing arenes.⁹⁰

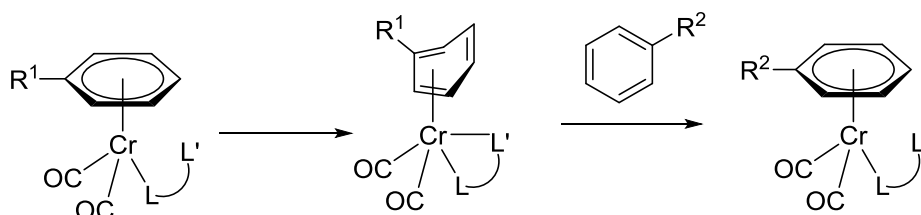
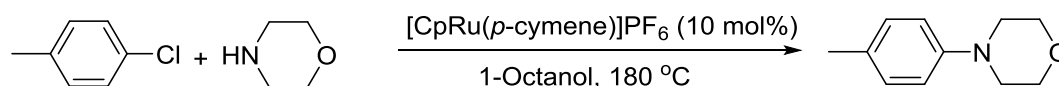


Figure 3.6: Temporary chelation of ligand side chain in arene exchange

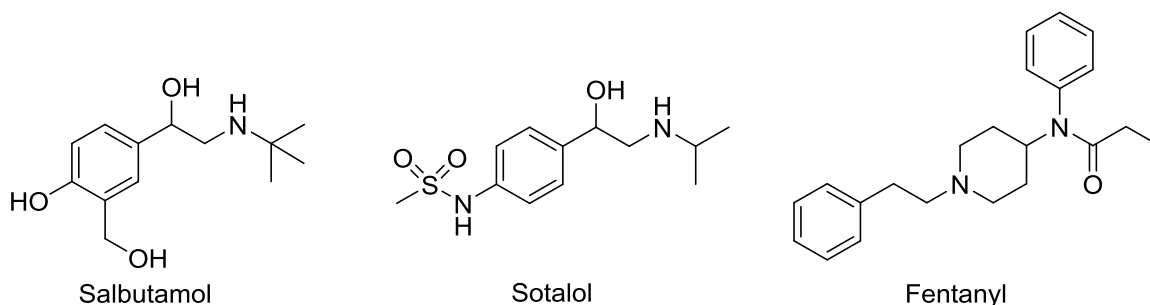
As mentioned in Chapter 1, Otsuka *et al.* published the first example of the ruthenium catalysed $\text{S}_{\text{N}}\text{Ar}$ reaction between a non-activated arene and an amine using $[\text{Ru}(\text{cod})(2\text{-methylallyl})_2]$ as the catalyst precursor (**Figure 1.19**).^{32,33}

Walton and Williams reported the $[\text{RuCp}(p\text{-cymene})]\text{PF}_6$ catalysed $\text{S}_{\text{N}}\text{Ar}$ reaction between 4-chlorotoluene and morpholine (**Figure 3.7**). After 7 days the reaction was shown to go to 75 % conversion, leaving the reaction for a total of 14 days results in 90 % conversion. Arene exchange is thought to be the rate determining step, so it was investigated whether adding a pendant ligand would improve the rate of exchange. Promising results were seen with an ethyl pyridine tether on the Cp ring, with increased rate of exchange of *p*-cymene for hexamethylbenzene compared with no tether. Unfortunately, the complex demonstrated no increase in activity in the catalytic reaction.⁹¹

Figure 3.7: [RuCp(*p*-cymene)]PF₆ catalysed reaction

3.1.2 Activation of styrene

The product obtained from the anti-Markovnikov addition of an amine to styrene is a β -arylethylamine. This is a privileged structure within the pharmaceutical industry as it is found in many drugs. Some examples are Salbutamol, which is an asthma treatment, Sotalol, used in the treatment of heart conditions and Fentanyl which is used as pain relief, as well as many other pharmaceuticals (**Figure 3.8**). Styrene can be activated in a number of ways, which include: activation through the alkene and η^6 -binding to a metal centre.

Figure 3.8: Examples of β -arylethylamine structure

3.1.2.1 η^6 -Bound styrene

The activation of styrene to nucleophilic attack through η^6 -complexation to chromium species (Cr(CO)₃) was reported by Semmelhack *et al.* in 1980. A variety of carbon nucleophiles was used. The chromium complex was treated with addition of a nucleophile followed by addition of an electrophile. Finally decomposition of the complex gave the free arene (**Figure 3.9**), moderate to excellent yields of 43 to 100% were obtained.²⁸

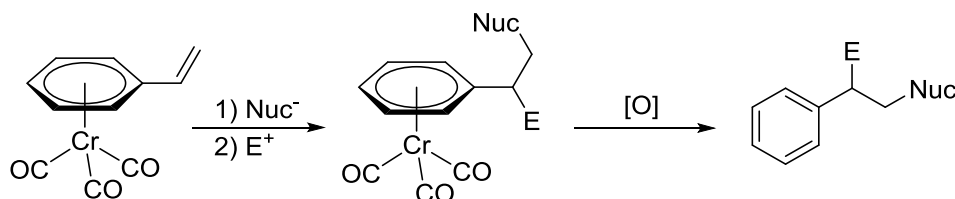


Figure 3.9: Chromium facilitated addition to styrene

As mentioned in Chapter 1, Takaya and Hartwig carried out a mechanistic study into the anti-Markovnikov hydroamination of vinylarenes through η^6 -binding to ruthenium complex (**Figure 1.21**).³⁴

As the $[\text{Ru}(\text{cod})(2\text{-methylallyl})_2]$ precursor used by Otsuka in the example above (from **Figure 1.19**) was thermally sensitive, Otsuka *et al.* investigated developing a system with a more stable precursor. Using $[\text{RuCl}_2(\eta^6\text{-benzene})]_2$ as a precursor with AgOTf to introduce OTf^- as the counterion, a series of ligands was screened, with DPPPEnt giving the highest yields and selectively for β -addition (**Figure 3.10**). Using these conditions, moderate yields of 15 to 75% were obtained for a series of secondary amines. The reaction was also shown to work with α -methylstyrene, leading to the generation of a chiral centre. Chiral ligands were investigated to determine if the reaction could be carried out enantioselectively. The use of (S)-xylylBINAP as ligand, allowed for enantioselectivity of up to 75%.⁹²

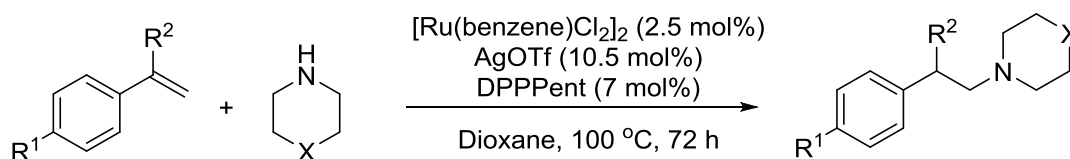


Figure 3.10: Selective addition to styrene

3.1.3 Synthesis of η^6 -arene metal complexes and their precursors

Due to their use in the activation of arenes, the synthesis of η^6 -arene metal complexes is of interest. As mentioned previously $[\text{RuCp}(\eta^6\text{-arene})]\text{PF}_6$ can be prepared from $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$, this has led to the development of several methods for the preparation of $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$.

Gill and Mann carried out studies into the photochemical properties of the $[\text{RuCp}(\eta^6\text{-benzene})]^+$ cation, these studies led to the discovery that irradiating $[\text{RuCp}(\eta^6\text{-benzene})]^+$ in acetonitrile gave the $[\text{RuCp}(\text{MeCN})_3]^+$ cation. The acetonitrile can be substituted for an arene, by heating $[\text{RuCp}(\text{MeCN})_3]^+$ in the presence of the desired arene.⁹³ Using Zelonka and Baird's method to synthesise $[\text{RuCp}(\eta^6\text{-benzene})]\text{Cl}$,⁹⁴ a three step synthesis of $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ was developed from ruthenium chloride (**Figure 3.11**). Initially the dimer $[\text{RuCl}_2(\eta^6\text{-benzene})]_2$ was synthesised from ruthenium chloride and 1,3- or 1,4-cyclohexadiene. The benzene-

Ru-Cp sandwich was then synthesised using thallium cyclopentadiene to introduce the Cp ring, followed by ammonium hexafluorophosphate for the counterion. Irradiation of $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$ led to the desired product.

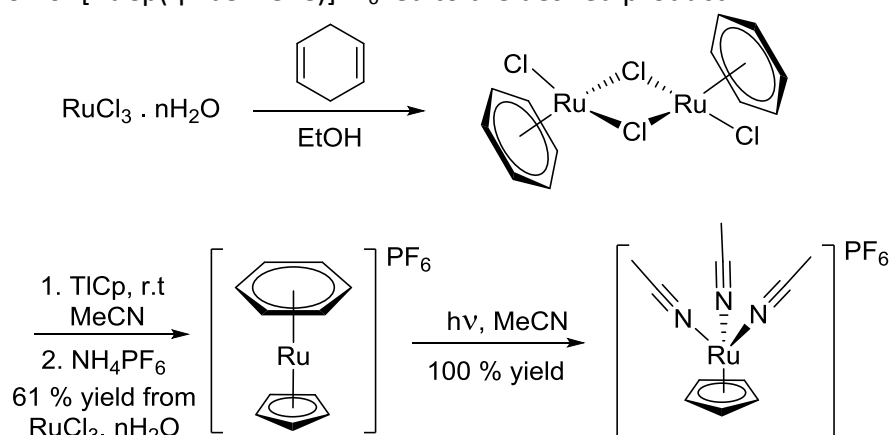


Figure 3.11: Synthesis of $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$

This method was further developed by Trost and Older by removing the need to use the highly toxic thallium. The Cp ring was introduced into the complex using freshly cracked cyclopentadiene and potassium carbonate heated at 60 °C (**Figure 3.12**), followed by addition of ammonium hexafluorophosphate for the counterions, as in the previous method.⁹⁵

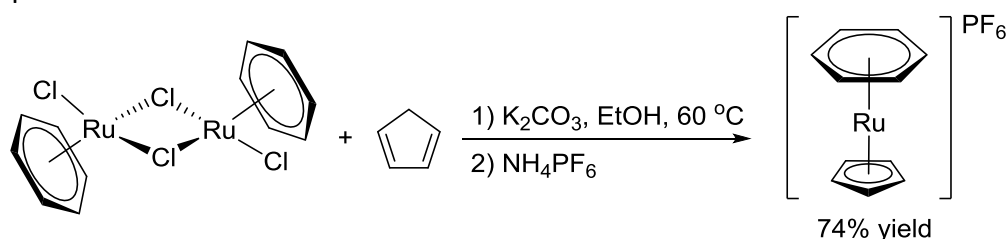
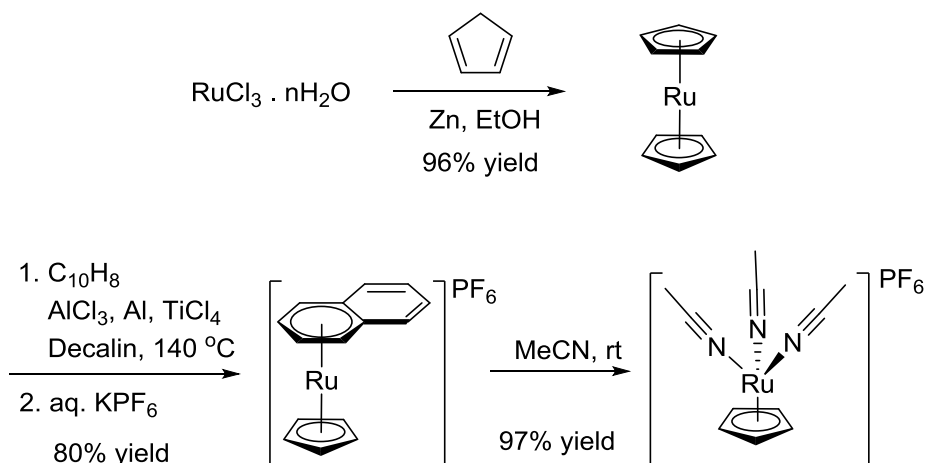
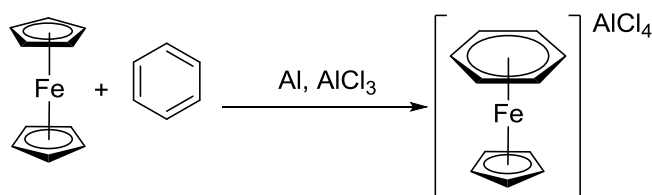


Figure 3.12: Alternative route to $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$

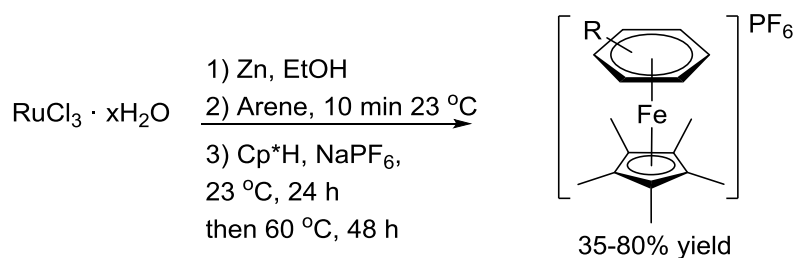
A different approach to the synthesis of $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ from ruthenium chloride was developed by Kündig and Monnier. In this method ruthenium chloride is transformed into $[\text{RuCp}_2]$ using cyclopentadiene and zinc. Then one of the Cp rings was substituted by naphthalene, using aluminium chloride, aluminium powder and titanium chloride, followed by introduction of the PF_6 counterion. Vigorous stirring at room temperature of the naphthalene complex with acetonitrile afforded the desired product $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (**Figure 3.13**).⁹⁶

Figure 3.13: Alternative route to $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$

Nesmeyanov *et al.* developed a synthesis of arene-iron-Cp sandwich complexes from ferrocene. Heating ferrocene in the presence of aluminium chloride, aluminium and the desired arene to between 70 °C and 190 °C afforded the desired product (**Figure 3.14**). Introduction of the counterion was achieved by the addition of ammonium hexafluorophosphate.⁹⁷

Figure 3.14: Synthesis of $[\text{FeCp}(\eta^6\text{-benzene})]\text{AlCl}_4$

A one-pot synthesis of $[\text{RuCp}^*(\eta^6\text{-arene})]\text{PF}_6$ from ruthenium chloride was reported by Schmid *et al.* The method involves the addition of zinc dust to ruthenium chloride, followed by the addition of an arene, and finally Cp^*H and sodium hexafluorophosphate. The reaction mixture was then stirred for 1 day at room temperature followed by 2 days at 60 °C to yield the product (**Figure 3.15**). It was demonstrated that various functionalised arenes could be used, although lower yields were obtained for arenes with more bulky groups.⁹⁸

Figure 3.15: One-step preparation of $[\text{RuCp}(\eta^6\text{-arene})]\text{PF}_6$

The preparation of complexes with molybdenum, along with the earlier mentioned $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ was achieved by Kündig and others. $[\text{Mo}(\eta^6\text{-benzene})(\text{CO})_3]$ was synthesised from $\text{Mo}(\text{CO})_6$ using benzene and ethyl formate in decalin at 240°C for 40 hours. Arene exchange was achieved by stirring $[\text{Mo}(\eta^6\text{-benzene})(\text{CO})_3]$ with trimethylphenylsilane in THF at room temperature for 2 hours, to give the product in quantitative yields (**Figure 3.16**). With other arenes, only partial exchange was observed under these conditions and it was found that removal of the volatiles and addition of further THF and arene led to complete conversion.⁹⁹

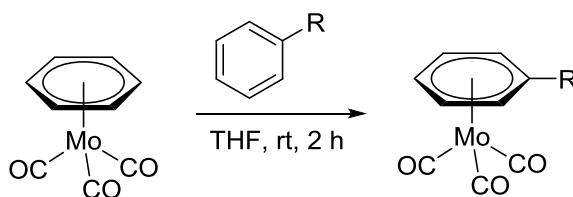


Figure 3.16: Arene exchange on molybdenum complexes

The synthesis of η^2 -diphosphine(η^6 -*p*-cymene)ruthenium(II) complexes was reported by Chaplin and others. The complexes with a pendant diphosphine ligand were prepared by the substitution of a labile acetonitrile group on $[\text{RuCl}(\eta^6\text{-p-cymene})(\text{NCMe})\text{L}]$ ($\text{L} = \text{PPh}_3$ or Cl) with a diphosphine. The diphosphine can bind either η^1 or η^2 by displacing L . When $\text{L} = \text{Cl}$ a cationic complex with a chloride counterion is prepared (**Figure 3.17**). The use of methanol favours the coordination of both the phosphines. Higher temperatures were needed when the chelation involved the substitution of a PPh_3 ligand compared with the temperature needed for substitution of a chloride ligand.¹⁰⁰

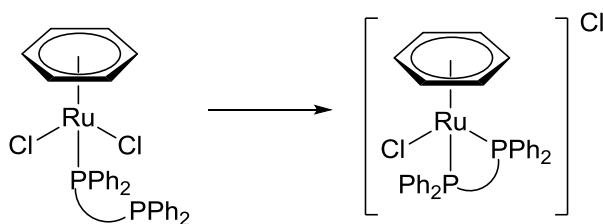


Figure 3.17: Chelation of diphosphine ligand

The synthesis of $[\text{RuCp}^*(\eta^6\text{-arene})]\text{Cl}$ *via* three different aqueous routes was developed by Fairchild and Holman in 2007. Each route starts with the cubic structured $[\text{Ru}(\mu_3\text{-Cl})\text{Cp}^*]_4$ (**Figure 3.18**) and proceeds in one step to the product. These methods produce no byproducts, require little workup and can be used with

most simple arenes. Two of the routes take advantage of microwave irradiation in the presence of an arene with water as the solvent, resulting in a clean reaction to the product. The methods differ as, one uses an excess of arene whereas the other uses stoichiometric arene and a mixture of THF:water (1:2) as the solvents. The third method involves the room temperature reaction of $[\text{Ru}(\mu_3\text{-Cl})\text{Cp}^*]_4$ dissolved in the minimum amount of acetonitrile with an arene in acetonitrile:water (1:16). This method allows for the use of arenes which are heat sensitive and cannot be used in a microwave reaction. All three methods produce $[\text{RuCp}^*(\eta^6\text{-arene})]\text{Cl}$ in near quantitative yields, as $[\text{Ru}(\mu_3\text{-Cl})\text{Cp}^*]_4$ is water soluble this widens the scope of reaction for these type of compounds.¹⁰¹

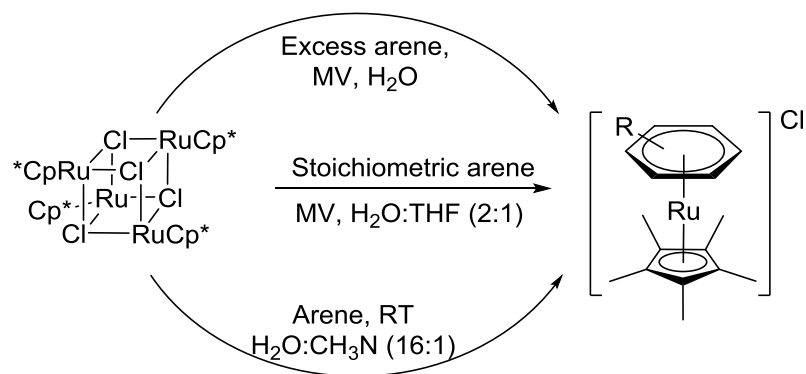


Figure 3.18: $[\text{RuCp}^*(\eta^6\text{-arene})]\text{Cl}$ from $[\text{Ru}(\mu_3\text{-Cl})\text{Cp}^*]_4$

This work was further developed, by investigation of the addition of a functional group on to the Cp^* ligand. $[\text{Ru}[(\eta^6\text{-C}_5\text{Me}_4\text{CH}_2)\text{Cl}(\mu\text{-Cl})]_2]$ is heated in acetonitrile in the presence of a nucleophile (water, alcohol, alkoxide or amine) and an arene. This results in the formation of $[\text{Ru}(\eta^5\text{-C}_5\text{Me}_4\text{CH}_2\text{R})(\eta^6\text{-arene})]^+$ ($\text{R} = \text{RH}$, OR or NR^1R^2) (Figure 3.19). The chelating group on the Cp ring can act as a pendant group and also bind to the metal centre.¹⁰²

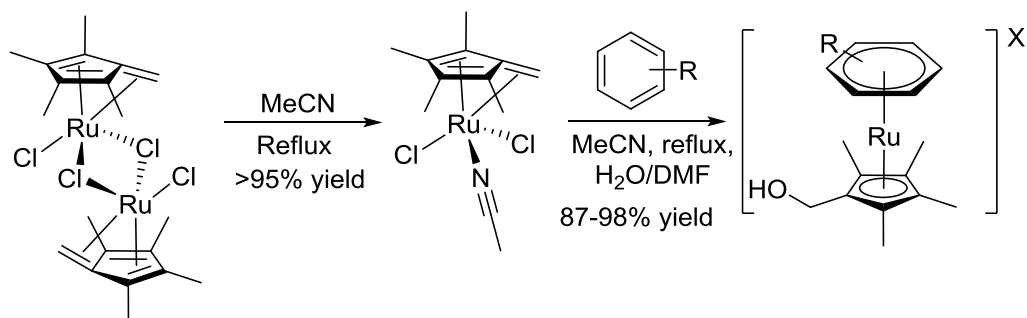


Figure 3.19: Synthesis of $[(\eta^5\text{-C}_5\text{Me}_4\text{CH}_2\text{OH})\text{Ru}(\eta^6\text{-arene})]^+$

Photolysis plays a key role in the chemistry of $[\text{MCp}(\eta^6\text{-arene})]$ species for metals such as ruthenium and iron. Photolysis is used in the synthesis of $[\text{RuCp}(\text{MeCN})_3]$ as found by Mann and Gill, which is a valuable precursor for many $[\text{RuCp}(\eta^6\text{-arene})]$ sandwich complexes.⁹³ Mann and Gill also investigated the photolysis reactions of iron-sandwich complexes. Arene exchange was promoted by visible light in DCM to give complete exchange of *p*-xylene for hexamethylbenzene after 5 hours (**Figure 3.20**). Substitution of *p*-xylene for three ligands was also demonstrated to be promoted by visible light, to give $[\text{RuCpL}_3]$ where $\text{L} = p\text{-CNPhCH}_3$, $\text{P}(\text{OPh})_3$ or CO , in a clean reaction carried out at room temperature.^{103,104}

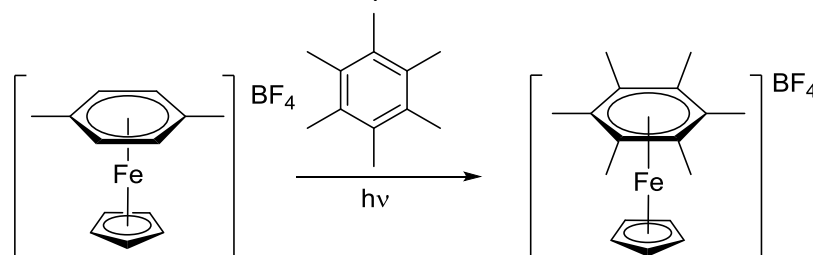


Figure 3.20: Substitution of *p*-xylene for hexamethylbenzene

This work was developed more recently by Aranaes and Astruc, it was demonstrated that a large variety of ‘piano stool’ iron complexes $[\text{FeCpL}^1\text{L}^2\text{L}^3]^+$ are accessible from ferrocene in two steps. The initial step of substituting a Cp ring for an arene is followed by a photolysis reaction in visible light, to substitute the arene for alternative ligands (**Figure 3.21**).¹⁰⁵

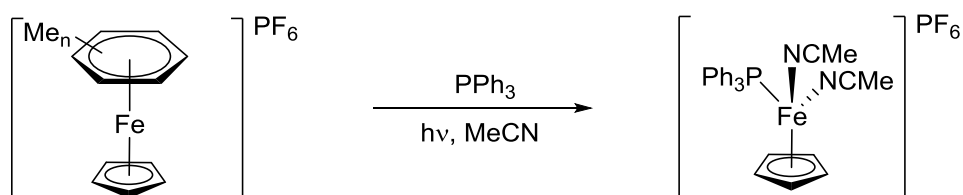


Figure 3.21: ‘piano stool’ iron complexes

Mori and Mochida reported the relationship between a series of complexes prepared from $[\text{RuCp}(\text{MeCN})_3]$ and 1,2-disubstituted benzene ligands, which can bind in different ways, depending on the conditions the complex is formed under (**Figure 3.22**). The chelating groups (E) were either secondary amines, ethers or thioethers, in the combination of NN, OO, SS, SO and SN. It was observed the ligands with harder donor atoms (O) tended to give the η^6 -arene complex, whereas the ligands with softer donor atoms (S) tended to give the chelated product. The

ligands containing nitrogen gave both products, with the kinetic product being the chelating complex and the thermodynamic product the sandwich complex.¹⁰⁶

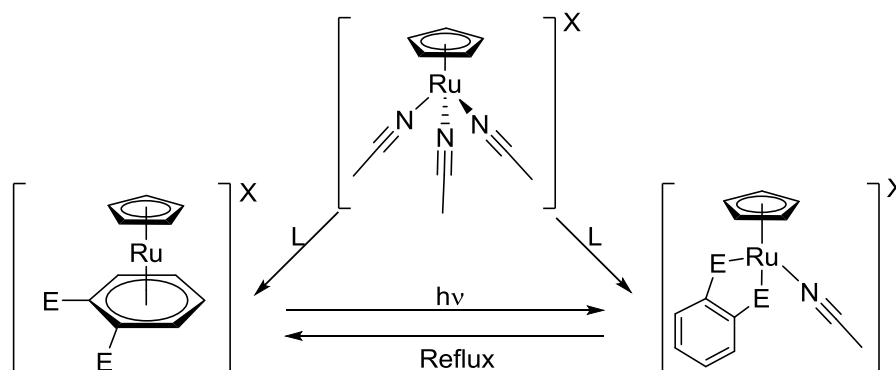


Figure 3.22: Reactions between $(\text{MeCN})_3\text{RuCp}$ and 1,2-disubstituted ligand

Styrene, an arene of interest in this work, has been shown to have photolytic activity, Johnston and Schepp reported the reactivity of styrene radical cations generated by laser flash photolysis. **Figure 3.23** shows the reactions explored. The radical cation reacted with nucleophile in the form of anions such as azide, chlorine and bromine. Reactions of styrene with alcohols, amines and pyridines occurred *via* a series of different mechanisms depending on the substrate. Reaction of the styrene radical cation with an alkene led to cycloaddition and quenching of the radical to give cyclobutane.¹⁰⁷

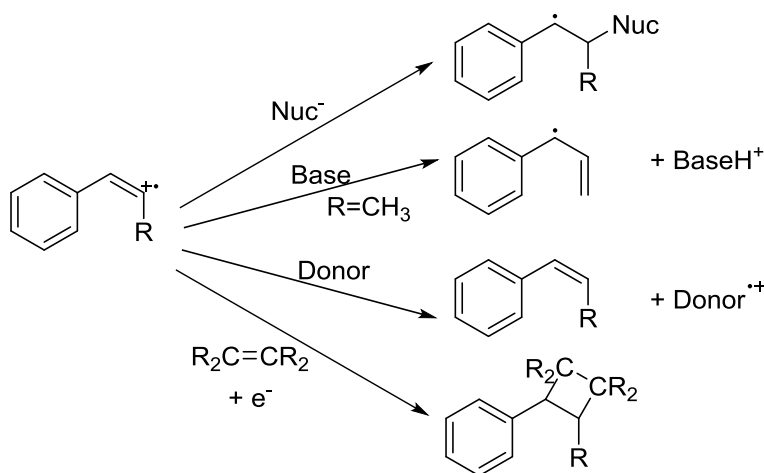


Figure 3.23: Reaction with styrene radical cation

The activation of arene through η^6 -binding to metals has proven to be valuable, but there are few examples of reactions being carried out catalytically. Photolysis has

also shown to play a key role in several of the examples, and it was hoped to exploit both of these in the development of a new catalytic reaction.

3.2 Aim and Objectives

As industry looks towards more efficient and sustainable processes, the development of new methods to catalyse chemical reactions is an essential area of modern research.

The activation of arenes through η^6 -binding to a metal will be exploited to change the reactivity of arenes and make them susceptible to be attacked by nucleophiles. Through this activation it is envisioned a catalytic cycle (**Figure 3.24**) can be developed for the following reactions:

- Nucleophilic addition to styrene
- Diels–Alder reactions with styrene
- S_NAr reaction with aryl halides

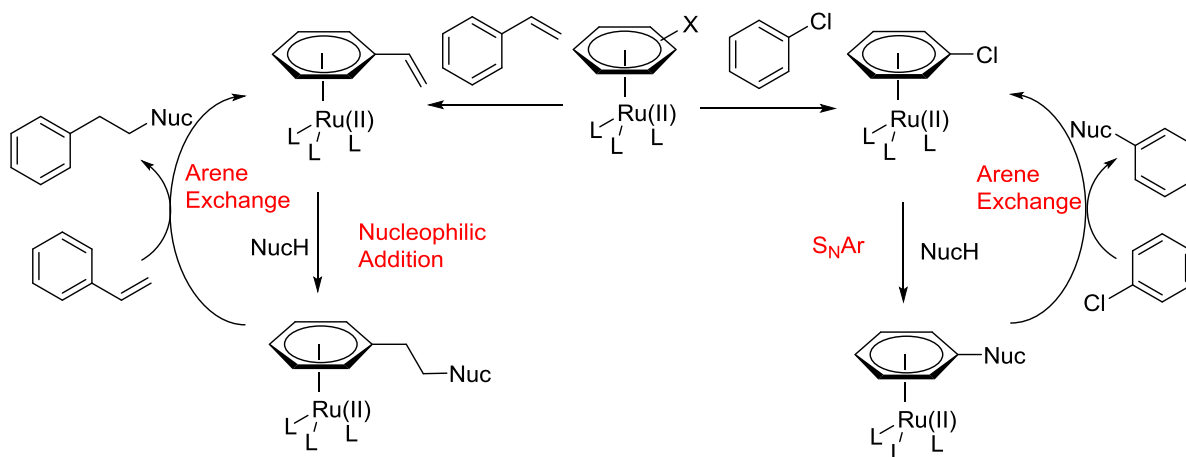


Figure 3.24: : Proposed catalytic scheme

3.3 Results and discussion

The method reported by Cambie and others was used to synthesise the $[\text{RuCp}(\eta^6\text{-arene})]\text{PF}_6$ species (**3.5**).⁸⁹ The simple route of heating the desired arene with $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (**3.4**) in DCE can give a wide variety of sandwich complexes in good yields. Trost and Older's three step method to $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ from ruthenium chloride was chosen, as it was relatively straightforward and gave the product in good yields (**Figure 3.25**).⁹⁵

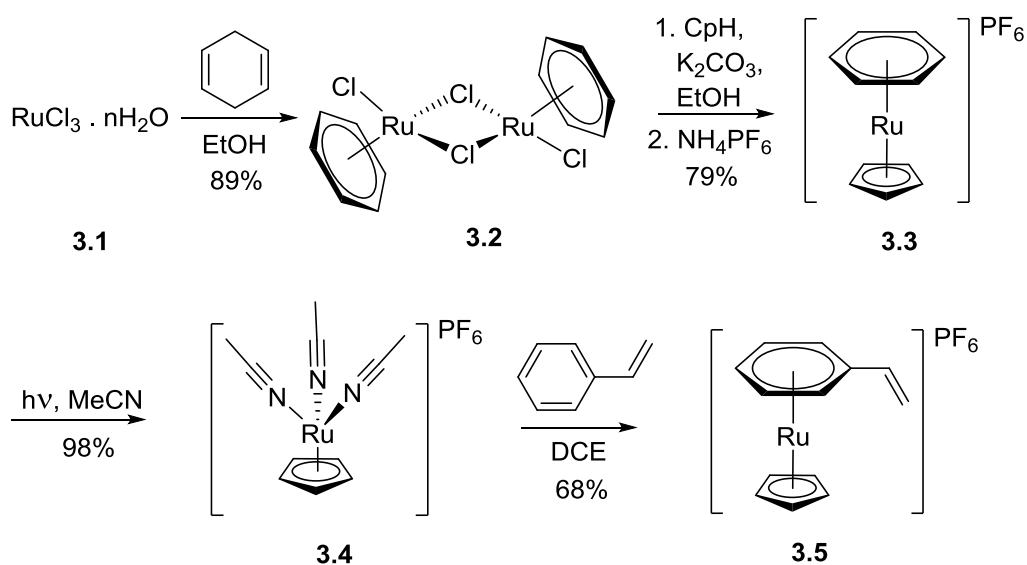


Figure 3.25: Synthesis of $[\text{RuCp}(\eta^6\text{-arene})]\text{PF}_6$

Ruthenium chloride was heated to reflux in methanol with 1,4-cyclohexadiene to give the dimer **3.2** in 89 % yield. The dimer was then reacted with freshly cracked cyclopentadiene at 60 °C, to yield the sandwich complex **3.3**, ammonium hexafluorophosphate was used to introduce the PF_6 counterion with an overall yield of 79 %. The sandwich complex was then irradiated with a 400 W medium pressure mercury lamp in acetonitrile, which led to the displacement of the benzene ligand with three acetonitrile ligands (98% yield). The $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (**3.4**) could then easily be converted into a variety of sandwich complexes through heating the complex in DCE in the presence of the desired arene, styrene gave a 68 % yield.

3.3.1 Nucleophilic addition to styrene

Although the overall aim is to achieve a catalytic cycle, as this is a relatively new area and the success of the reaction with these complexes was mainly unknown. It was decided initially to carry the reaction out stoichiometrically in Ru. Initial

investigations were targeted towards reactions on the η^6 -bound arenes to determine if reactions with these substrates were feasible before the complete catalytic cycle was explored.

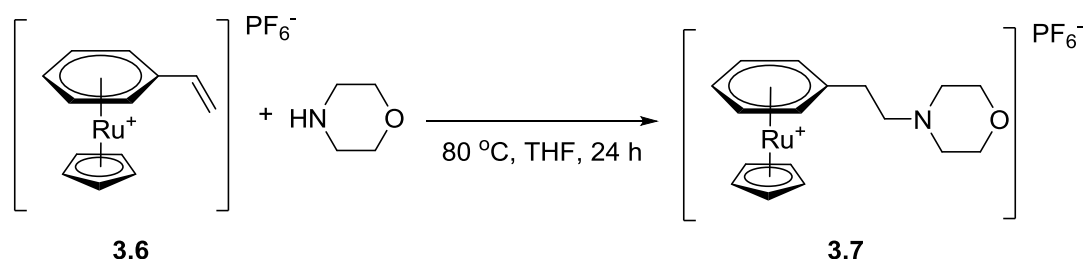


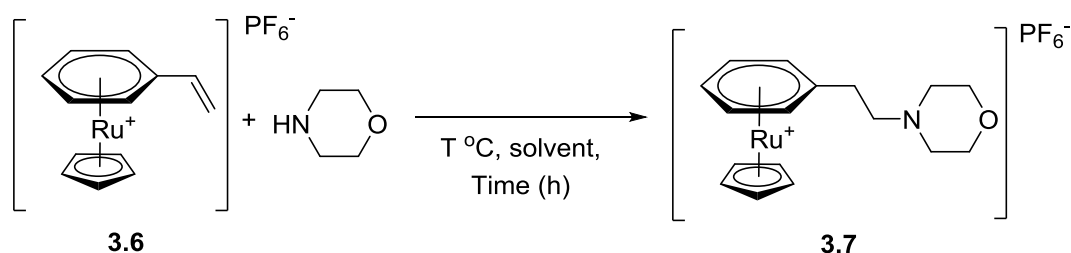
Figure 3.26: Nucleophilic addition to styrene-Ru sandwich complex

An initial reaction of the styrene sandwich complex $[(\text{RuCp}(\eta^6\text{-styrene}))\text{PF}_6]$ (**3.6**) with morpholine in THF at 80°C for 24 hours,³⁴ gave a clean reaction with complete consumption of the starting material **3.6** (Figure 3.26). Addition took place only on the terminal carbon of the alkene, to give solely the anti-Markovnikov product **3.7**. After this initial promising result, optimisation of the reaction conditions was carried out.

The reaction was performed in a series of solvents: THF, DCE, toluene, acetonitrile, DCM and diethyl ether. As it was thought the presence of acetonitrile would be needed in the catalytic cycle, it was included in the solvent screen to see if the reaction proceeds in it. No reaction was observed in toluene (Table 3.1, entry 4) and diethyl ether (Table 3.1, entry 7). It is thought this may be due to insolubility of complex **3.6** in these solvents. For the other four solvents the reaction was carried out at 20°C , 40°C and 60°C (excluding DCM) and monitored by TLC. No reaction was observed in all solvents at room temperature. At 40°C some conversion into the product **3.7** was observed in DCM, although after 24 hours only 57% conversion was achieved (Table 3.1, entry 6). As the boiling point of DCM is 39°C and a higher temperature was needed to increase the rate of reaction, it was decided to focus on the other three solvents. At 60°C , reactions proceeded in THF, DCE and acetonitrile (Table 3.1, entry 1, 2 and 5). Although DCE gave the highest yield after 6 hours (Table 3.1, entry 3), it was decided to avoid chlorinated solvents. In this case the conversion was not deemed to be a considerable improvement over the other solvents; therefore it was decided to focus on the use of THF. It was promising for

the catalytic cycle (see **Section 3.3.5**) to see that the reaction also proceeded in acetonitrile.

Table 3.1: Solvent and temperature screen



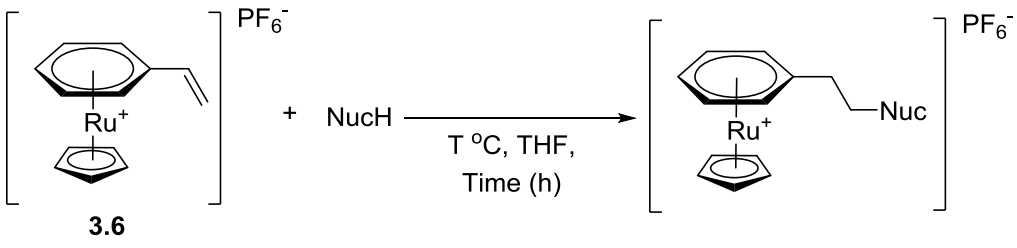
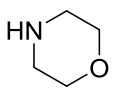
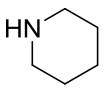
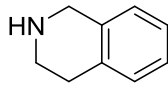


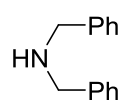
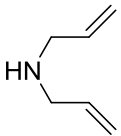
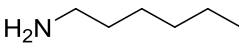
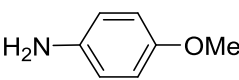
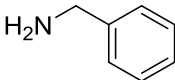
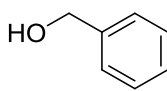
Entry	Solvent	20 °C (%) ^[a]	40 °C (%) ^[a]	60 °C (%) ^[a]
1	THF	nr	nr	50% (6 h)
2				100% (24 h)
3	DCE	nr	nr	71% (6 h)
4	Toluene	nr	nr	nr
5	Acetonitrile	nr	nr	67% (6 h)
6	DCM	nr	57% (24 hr)	-
7	Diethyl ether	nr	nr	nr

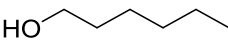

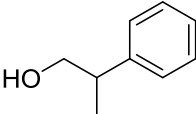
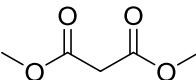
Conditions: 0.012 mmol [(RuCp(η⁶-styrene)]PF₆, 0.018 mmol morpholine, 0.2 mL solvent. ^[a] Conversions determined by analysis of ¹H NMR spectra.

Using these conditions, 60 °C in THF for 24 hours, the scope of the reaction was then explored (**Table 3.2**). Reactions with cyclic secondary amines proceeded to complete conversion to the corresponding β-arylethylamine, morpholine, piperidine, 1,2,3,4-tetrahydroquinoline and pyrrolidine, giving **3.7**, **3.8**, **3.9** and **3.10**, respectively (**Table 3.2**, entry 1-4). Disappointingly, even with the temperature increased to 80 °C, no reaction was seen for acyclic secondary amines diethylamine (**Table 3.2**, entry 5) and diallylamine (**Table 3.2**, entry 7), and a conversion of only 21% with dibenzylamine to give **3.12** was observed (**Table 3.2**, entry 6). It is thought this may be due to the fact that acyclic secondary amines are more sterically demanding than cyclic secondary amines. Due to the constrained nature of cyclic secondary amines the functional group is restricted in movement, resulting in the nitrogen lone pair being more available for nucleophilic attack. Whereas in acyclic

amines the functional groups have free rotation, this results in a less nucleophilic nitrogen.

Table 3.2: Substrate scope of nucleophilic addition to styrene

<div style="text-align: center;">  <p>3.6</p> </div>					
Entry	Compound	Nucleophile	Temperature (°C)	Time (h)	Conversion (%) ^[a]
1	3.7		60	24	100
2	3.8		60	24	100
3	3.9		60	24	100
4	3.10		60	24	100
5	3.11		80	24	-
6	3.12		80	24	21
7	3.13		80	24	-
8	3.14		80	24	53
9	3.15		80	24	-
10	3.16		80	24	71
11	3.17		80	24	-

12	3.18		80	24	-
13	3.19		80	24	-
14	3.20		80	24	-
15	3.21		80	24	100 ^[b]

Conditions: 0.024 mmol [RuCp(η^6 -styrene)]PF₆, 0.036 mmol nucleophile, 0.5 mL solvent. ^[a] Conversions determined by analysis of ¹H NMR spectra. ^[b] 0.048 mmol Dimethyl malonate and 0.048 mmol sodium methoxide.¹

Primary amines required the temperature to be increased to 80 °C. Although even with this increase, complete conversion was not observed after 24 hours. Reaction of **3.6** with hexylamine gave **3.14** with 53% conversion (**Table 3.2**, entry 8) and 71% conversion with benzylamine to give **3.16** (**Table 3.2**, entry 10), further optimisation for primary amines may be possible. In the case of 4-methoxyaniline no reaction was observed (**Table 3.2**, entry 9). This is consistent with the less nucleophilic nature of anilines, as the lone pair of the nitrogen is less available due to delocalisation into the aromatic ring. As DCE had shown promise in the solvent screen, the reactions with primary amines were repeated in DCE, this resulted in a reduction in conversion.

Benzyl alcohol, 1-hexanol, ethanol and 2-phenyl-1-propanol were also investigated, but all proved unreactive (**Table 3.2**, entry 11-14). As alcohols are less nucleophilic than amines, this is not completely unsurprising. Finally, dimethyl malonate was used in the hope of opening up the potential for forming a carbon-carbon bond (**Table 3.2**, entry 15). An equivalent of sodium methoxide was added to activate the malonate by removal of an acidic proton on the central carbon. Encouragingly, complete conversion of the starting complex **3.6** was observed. An activating alkoxide and malonate carrying the same functional group were chosen, as transesterification may take place between one of the ester groups on the malonate and the alkoxide. Use of the same group ensures that a mixture of products is not obtained. Although complete conversion of the starting styrene complex was observed, on closer examination of the analytical data it was evident

that a side product had also been formed. Using mass spectrometry, it was determined to be the decarboxylation product **3.22** (**Figure 3.27**).

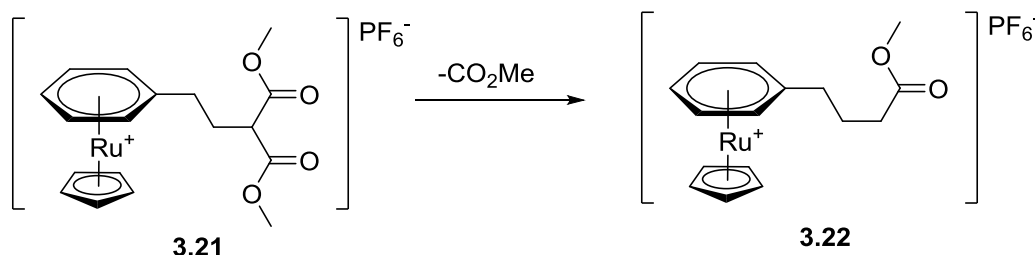


Figure 3.27: Side reaction with malonates

In all cases, the addition of the nucleophile was only observed at the terminal carbon of the styrene to give the anti-Markovnikov product, this was easily identifiable by the appearance of two distinct triplets in the ^1H NMR spectra. It is hypothesised that this is due to the cationic metal centre withdrawing the delocalised electron density of the ring. As the electrons of the alkene are delocalised into the ring, these electrons are also pulled towards the metal, which results in a polar double bond, with the β -carbon being assigned as δ^+ and the α -carbon δ^- (**Figure 3.28**). This leads to selective attack of the nucleophile at the β -carbon and production of only the anti-Markovnikov product.

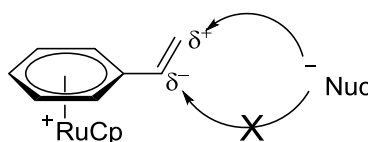


Figure 3.28: Proposed activation of Styrene-Ru complex

It is also thought that other nucleophiles could be employed, such as phosphorus containing compounds, to make phosphine ligands. This was not explored further at this point as this initial work was to determine the feasibility of the project and not to carry out a full substrate scope.

3.3.2 Diels–Alder reaction with styrene

After the success with the nucleophilic addition reaction, it was thought the alkene may also be activated towards Diels–Alder reaction, acting as a dienophile (**Figure 3.29**). As the Diels–Alder proceeds through the overlap of the highest occupied molecular orbital of the diene (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the dieneophile, it was thought complex **3.6** may behave as an electron

deficient dieneophile. Electron deficient alkenes are more reactive towards Diels–Alder cyclisation as the electron withdrawing group lowers the energy of the LUMO, reducing the energy gap between the HOMO and LUMO.

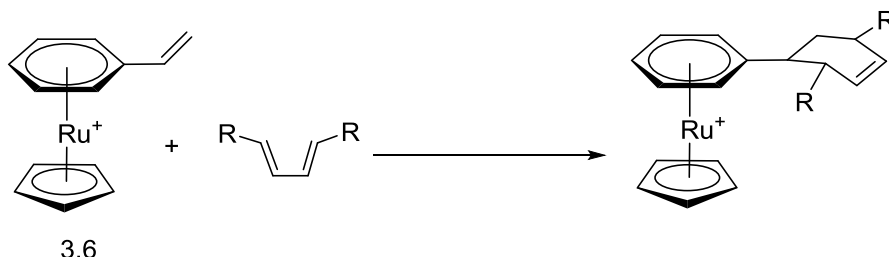
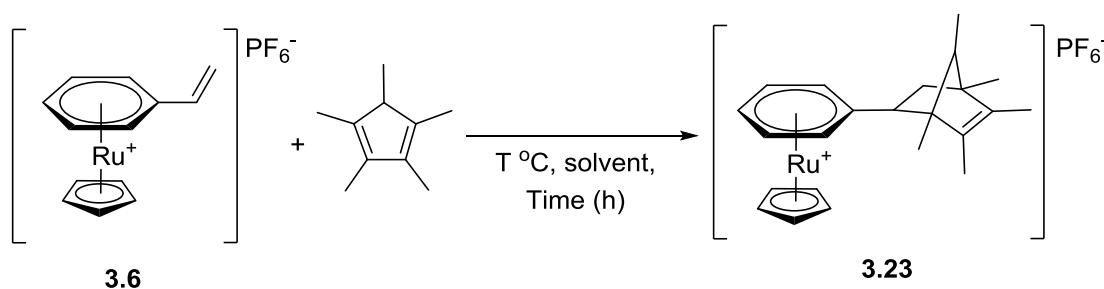


Figure 3.29: Diels–Alder reaction with styrene

1,2,3,4,5-Pentamethylcyclopentadiene was chosen as the diene to explore this reaction. Conversions were determined by analysis of the crude ¹H NMR spectra, through comparison of the Cp ligand's chemical shift, complete analysis of the crude NMR spectra was not carried out. The formation of the desired product was confirmed by the correct mass ion being found by high resolution mass spectrometry (HRMS). Initial conditions employed 1.5 equivalents of diene in THF at 60 °C for 24 hours (**Table 3.3**). Although only a 46% conversion into **3.23** was observed (**Table 3.3**, entry 1), this was a promising result as it demonstrated that the reaction was feasible. Increasing the temperature to 80 °C resulted in an increase of conversion to 83% (**Table 3.3**, entry 2). As the boiling point of THF of 66 °C, it was undesired to push the temperature any higher in this solvent. The earlier success of DCE for cyclic secondary amine, suggested it might be an alternative solvent for this reaction. At 80 °C in DCE a slightly improved conversion of 85% was obtained (**Table 3.3**, entry 3) The temperature was increased to 85 °C, which resulted in a conversion of 91% (**Table 3.3**, entry 4). Increasing the number of equivalents of diene from 1.5 to 1.75 and 2 equivalents had little effect on the conversion (**Table 3.3**, entry 5-6). It is hoped that due to the dipole of the alkene and the bulky nature of the sandwich complex that the reaction will be selective towards either the endo or exo product, although this was not determined in these feasibility reactions.

Table 3.3: Diels–Alder optimisation



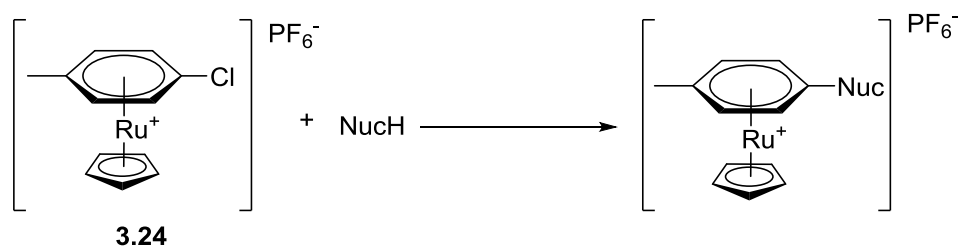
Entry	Solvent	Diene (equiv)	Temp. (°C)	Time (h)	Conv. (%) ^[a]
1	THF	1.5	60	24	46
2	THF	1.5	80	24	83
3	DCE	1.5	80	24	85
4	DCE	1.5	85	24	91
5	DCE	1.75	85	24	83
6	DCE	2	85	24	87

Conditions: 0.024 mmol $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$, 0.036–0.45 mmol 1,2,3,4,5-pentamethylcyclopentadiene, 0.5 mL solvent. ^[a] Conversions determined by analysis of ^1H NMR spectra.

So far, these reactions have only been carried out with styrene, it was hoped the use of other vinylarenes will be possible which would open up a large number of possible chemical structures, if a catalytic cycle could be developed.

3.3.3 $\text{S}_{\text{N}}\text{Ar}$ reactions with 4-chlorotoluene

Cambie *et al.* had reported the $\text{S}_{\text{N}}\text{Ar}$ reaction between $[\text{RuCp}(\eta^6\text{-chlorobenzene})]\text{PF}_6$ and a variety of nucleophiles (Figure 3.30).⁸⁹

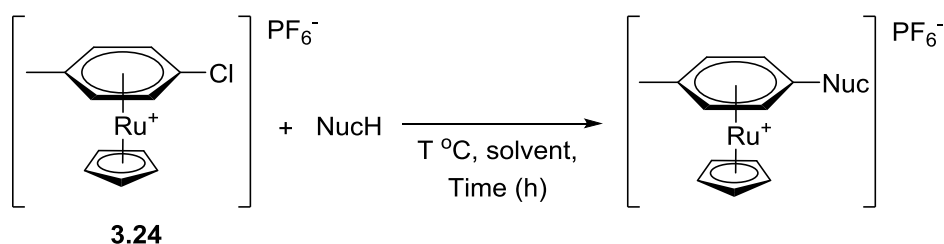
Figure 3.30: $\text{S}_{\text{N}}\text{Ar}$ reaction of 4-chlorotoluene

Different conditions were reported for morpholine and butylamine, although a large excess of amine was used in both instances. In the case of morpholine, 40 equivalents of amine were added and the reaction was heated at reflux in the dark for 24 hours. Whereas 13.5 equivalents of butylamine were used, along with the addition of acetic acid and the reaction was heated at reflux for 70 hours. Taking

these conditions into consideration and referring back to the conditions used for the nucleophilic addition, for butylamine, 10 equivalents of butylamine and 20 equivalents of acetic acid in THF at 80 °C for 24 hours. Under these conditions a conversion of 93% to **3.25** was observed (**Table 3.4**, entry 1). To determine the importance of the acetic acid, the S_NAr reaction with butylamine was repeated without the addition of acetic acid, the reaction showed a lower conversion of 39% (**3.25**).

The large excess of morpholine used in Cambie's procedure was not desirable for the reaction conditions planned for the catalytic cycle. The addition of fewer equivalents of amine was explored. Two equivalents of both amine and acetic acid were used, and after 24 hours, a conversion of 48% to **3.26** was observed (**Table 3.4**, entry 2). The reaction was repeated without acetic acid and a conversion to **3.26** of only 5.1 % was achieved. This suggests the reaction proceeds slower without the presence of acetic acid.

The reaction was also attempted using dimethyl malonate (**Table 3.4**, entry 3), with sodium methoxide. Whether conversion into product **3.27** had taken place was unclear by analysis of ¹H NMR spectra. Although the mass ion of the η⁶-bound RuCp product **3.27** was present in the mass spectrum, with the expected isotope distribution for a ruthenium complex, as mass spectrometry is not quantitative a conversion could not be obtained.

Table 3.4: S_NAr reactions

Entry	Compound	NucH	Temp. (°C)	Conv. (%) ^[d]
1	3.25		80	93 ^[a]
2	3.26		80	48 ^[b]
3	3.27		80	— ^[c]

^[a] 0.023 mmol [RuCp(η⁶-chlorobenzene)]PF₆, 0.23 mmol butylamine and 0.46 mmol acetic acid, 0.5 mL THF. ^[b] 0.023 mmol [RuCp(η⁶-chlorobenzene)]PF₆, 0.046 mmol butylamine and 0.046 mmol acetic acid, 0.5 mL THF. ^[c] 0.023 mmol [RuCp(η⁶-chlorobenzene)]PF₆, 0.046 mmol methylmalonate and 0.046 mmol sodium methoxide, 0.5 mL THF. ^[d] Conversions determined by analysis of ¹H NMR spectra.

As the S_NAr reaction with amines was already known, it was decided to focus on developing the catalytic cycle before further optimising the reaction and determining the full scope of this reaction.

3.3.4 Arene exchange

As a major aspect of the catalytic cycle is the exchange of the product arene for a molecule of the starting arene, achieving this exchange has been an important part of the research (**Figure 3.31**).

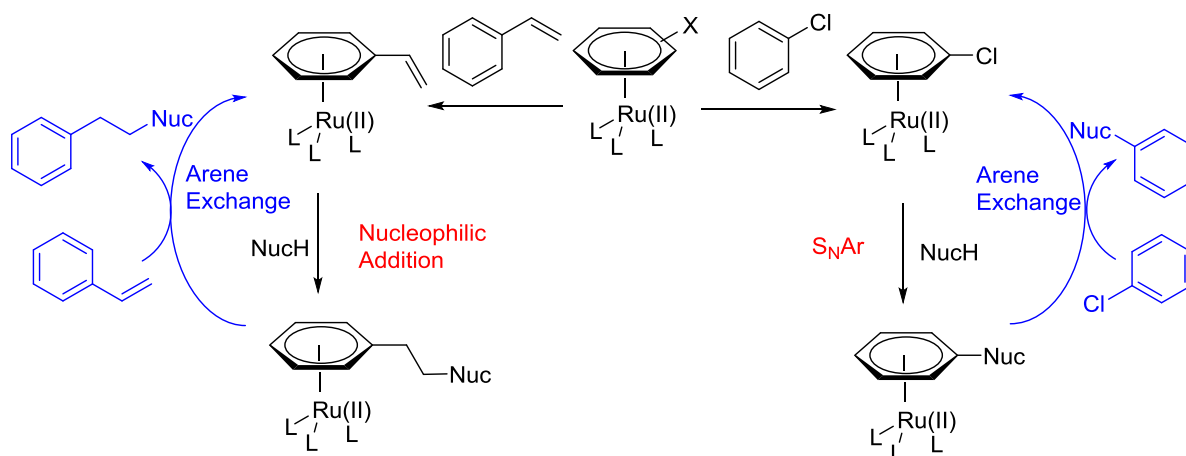


Figure 3.31: Proposed catalytic cycle

It was thought that the relationship shown in **Figure 3.32** between $[\text{RuCp}(\eta^6\text{-arene})]\text{PF}_6$ (**3.3**) and $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (**3.4**) could be exploited; where the arene exchange goes through $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (**3.4**) as an intermediate.

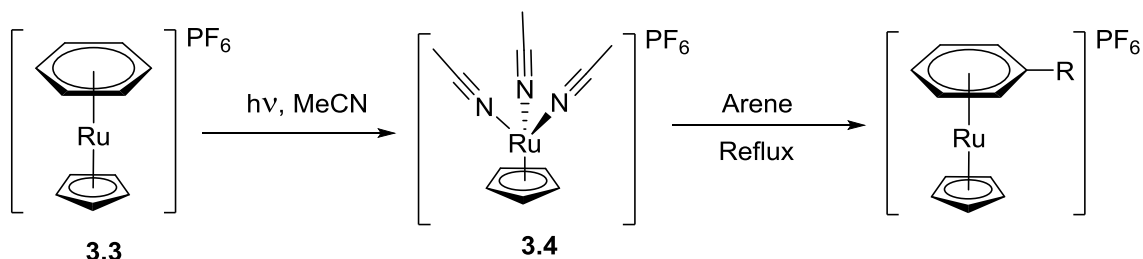


Figure 3.32: Ruthenium complexes

Exchange of the benzene on $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$ (**3.3**) with styrene was investigated. When acetonitrile was used as solvent, conversion into $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (**3.4**) was observed but no styrene coordination to ruthenium was detected (**Table 3.5**, entry 1). Changing the solvent ratio to mixtures of THF:acetonitrile and DCE:acetonitrile and the use of different concentrations of arenes along with $h\nu$ irradiation of the sample using a 400 Watt medium pressure mercury lamp, did not improve the arene exchange.

After some consideration it was proposed that heating the sample while it was irradiated may favour the exchange of the arenes. Irradiation of the arene-complex would lead to the acetonitrile intermediate, heating of this intermediate would afford exchange of the acetonitrile ligands for the new arene.

Table 3.5: Arene exchange conditions

3.2					3.6/3.24	
Entry	Solvent	mL ^[a]	Temp (°C)	Arene	Equiv ^[b]	Conv. (%) ^[c]
1	Acetonitrile	0.5	60		3	-
2	DCE	0.5	60		3	25
3	THF	0.5	60		3	30
4	THF	0.5	60		20	47
5	DCE	0.5	60		20	45
6	THF	0.5	80		20	-
7	THF	0.5	80		20	40
8	DCE	0.5	80		20	69

Conditions: 0.024 mmol [RuCp(η⁶-benzene)]PF₆, arene, 1 mL solvent. ^[a] All samples contain 0.5 mL of acetonitrile. ^[b] Equivalents with respect to [RuCp(η⁶-benzene)]PF₆. ^[c] Conversion calculated from proton NMR spectra.

As mentioned above, when the reaction was performed with just acetonitrile as the solvent, only conversion to [RuCp(MeCN)₃]PF₆ (**3.4**) was observed. Therefore it was decided to use a 1:1 ratio of acetonitrile with either THF or DCE. Using 3 equivalents of styrene, in acetonitrile/DCE a 25% exchange of arene to give **3.6** was observed, when the reaction was heated to 60 °C and irradiated for 16 hours (Table 3.5, entry 2). This promising result indicated that carrying out the arene exchange with this method was a viable route. When the same reaction was carried out in acetonitrile/THF a conversion of 30% into **3.6** was achieved (Table 3.5, entry 3). As it

was planned to carry the reaction out catalytically, it was decided to increase the number of equivalents of styrene to 20 equivalents with respect to $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$. Under these conditions an increase to 45% conversion into **3.6** was observed in acetonitrile/DCE (**Table 3.5**, entry 4). When the solvent was changed to acetonitrile/THF the conversion into **3.6** also increased from 30% to 47% (**Table 3.5**, entry 5). To try and improve these conversions further, the temperature of the reaction was then increased from 60 °C to 80 °C, in acetonitrile/THF with 20 equivalents of styrene (**Table 3.5**, entry 6). The proton NMR spectrum of the reaction mixture showed a complex mixture of products and it was attributed to photoinduced oligomerisation or polymerisation of styrene at high temperatures. This was disappointing as it indicated that for the reactions involving styrene, this method of catalysis may not be feasible.

It was decided to change the arene in the exchange reaction to 4-chlorotoluene as this was unlikely to undergo polymerisation and ^1H NMR spectra are easily interpreted due to the symmetrical nature of the product. The reaction at 80 °C in acetonitrile/THF was repeated using 20 equivalents of 4-chlorotoluene, a conversion into **3.24** of 40% was achieved (**Table 3.5**, entry 7). This result was further improved by using the same conditions with acetonitrile/DCE as the solvent, for which a conversion into **3.24** of 69% was observed (**Table 3.5**, entry 8).

Although arene exchange has been demonstrated to take place between benzene and styrene or 4-chlorotoluene, when the reaction with the nucleophile has taken place the electronics of the ring will be altered, the substituted arene may behave differently. In the case of the $\text{S}_{\text{N}}\text{Ar}$ reaction with an amine, an aniline is formed. As amine groups are strongly electron donating, the electron density of the ring will increase, which will lead to a stronger bond between the ring and metal centre. This may make the arene exchange unfavourable as the metal centre will form a stronger bond to the more electron rich arene. It may be difficult to push the reaction to 100% conversion, as the concentration of reacted arene increases; the metal is more likely to bind to the already reacted arene instead of the unreacted arene. $[\text{RuCp}(\eta^6\text{-}N\text{-methylaniline})]\text{PF}_6$ was synthesised to investigate this.

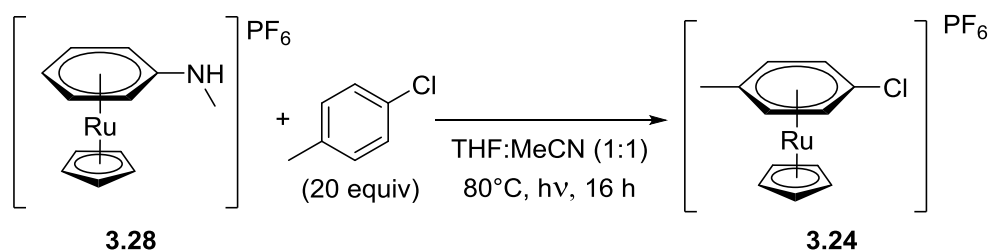


Figure 3.33: Attempted exchange of N-methylaniline

Complex **3.28** and 4-chlorotoluene were irradiated and heated at 80 °C in a 1:1 mixture of acetonitrile: THF for 16 hours (**Figure 3.33**). Interpretation of the ^1H NMR determined that no exchange to **3.24** had taken place. This result along with those with the attempted exchange with styrene would suggest that this method of exchange is not a viable route for the proposed catalytic cycle.

3.3.5 Catalytic cycle

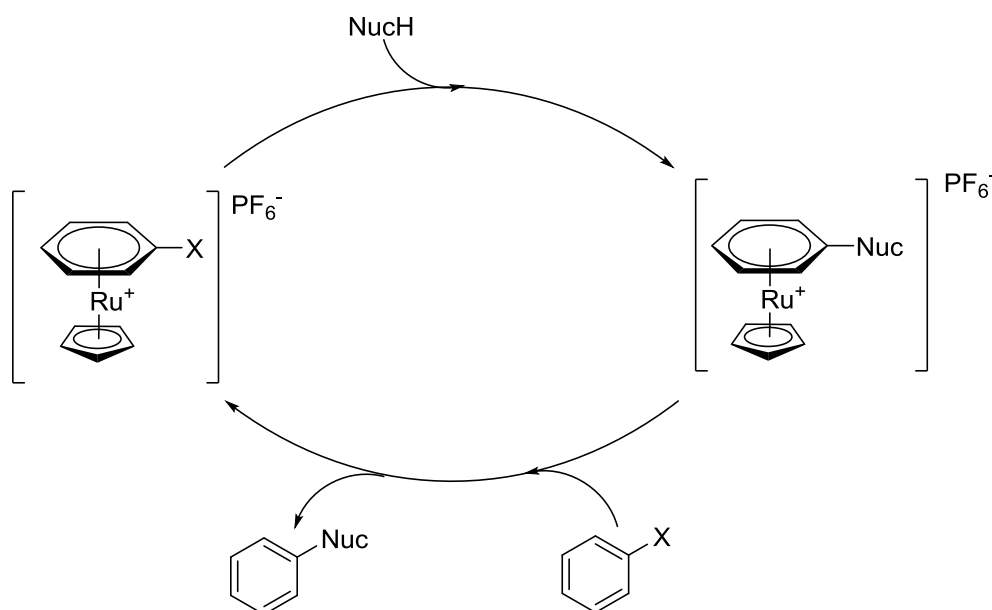


Figure 3.34: Hypothesised catalytic cycle

Disappointingly, attempts to carry out the reactions catalytically have thus far have proved unsuccessful (**Figure 3.34**). Although some interesting alternative reactions have been found during the investigation

Initial attempts to carry out a catalytic nucleophilic addition reaction were attempted between styrene and morpholine. A 10 mol% loading of $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$ (**3.3**) or $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$ (**3.6**) in DCE with 1 equivalent of styrene and morpholine was used, this was then irradiated for 16 hours. Promisingly, it appeared from interpretation of the ^1H NMR spectrum of the $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$

(**3.6**) reaction, that along with the product from the nucleophilic addition to the bound styrene, there was unbound β -arylethylamine product. On inspection of the $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$ (**3.3**) reaction, both the unbound β -arylethylamine product and Ru-bound benzene were observed in the ^1H NMR spectrum. Although there was no evidence of bound styrene or bound β -arylethylamine product, indicating that no arene exchange had taken place. This suggested that although a product had been formed, the ruthenium did not play a role in its production. Further evidence for this was provided by performing a reaction between styrene (**3.29**) and morpholine in DCE, with no ruthenium present and irradiating the reaction for 16 hours. After removal of the solvent, excess styrene and morpholine, a complex proton NMR spectrum was obtained. Although it is not completely clear what is occurring in the reaction, it is considered feasible that a photoinitiated nucleophilic addition of morpholine to styrene has taken place to give **3.30** (Figure 3.35), similar to the reactions reported by Johnston and Schepp.¹⁰⁷

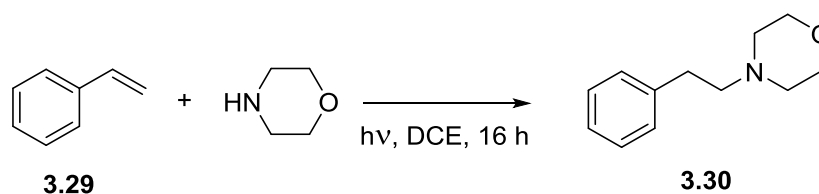


Figure 3.35: Proposed reaction of styrene and morpholine

This fact and polymerisation of the styrene, has determined that the use of a photocatalytic method is not a practical route to obtain β -arylethylamines from styrene. Although activation of styrene for nucleophilic attack through η^6 -binding in $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$ (**3.6**) has proved successful, development of an alternative method for cleavage and exchange of the product is needed.

Due to the side reaction which took place when styrene was irradiated, 4-chlorotoluene was also investigated. When the reaction was performed using the conditions mentioned above from the $\text{S}_{\text{N}}\text{Ar}$ reaction with irradiation of the reaction, with $[\text{RuCp}(\eta^6\text{-4-chlorotoluene})]\text{PF}_6$ (**3.24**), 4-chlorotoluene, butylamine and acetic acid. Mass spectrometry showed that the bound product **3.25** had been formed, but no free product was present. It was decided to determine if the reaction would proceed without acetic acid, $[\text{RuCp}(\eta^6\text{-4-chlorotoluene})]\text{PF}_6$ (**3.24**) and 10

equivalents butylamine were heated in DCE/acetonitrile to 80 °C and irradiated for 16 hours, a 89% conversion into **3.25** was observed (**Figure 3.36**). As discussed earlier, when the reaction is heated without addition of acetic acid, the S_NAr reaction only proceeds to 39% conversion after 24 hours.

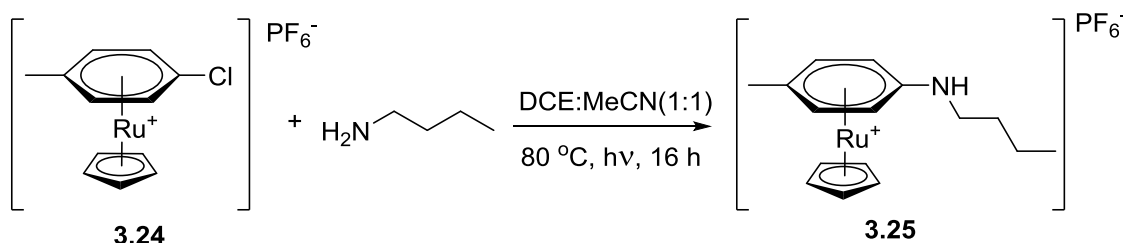


Figure 3.36: S_NAr reaction without acetic acid

To determine if a combination of heating and irradiating the reaction or just irradiating the reaction was enabling the substitution to take place without the acetic acid, the reaction was repeated without heating. A 79% conversion was obtained, which would suggest that irradiating the sample is promoting the S_NAr reaction. A background rate check was carried out to ensure that the ruthenium was playing a role in the reaction. No reaction was observed when 4-chlorotoluene and butylamine were irradiated together, which indicates the arene needs to be activated in the first place for the reaction to proceed via photolysis.

While interpreting the ^1H NMR data for the above reactions, it was noted that there were larger amounts of unreacted starting butylamine still present in the reaction mixture. As the boiling point of n-butylamine is 79 °C it was thought this would be removed with the removal of the solvent. After leaving the sample under high vacuum, the butylamine was still present in the ^1H NMR spectrum.

After consideration of what was in the reaction mixture; $[\text{RuCp}(\eta^6\text{-4-chlorotoluene})]\text{PF}_6$ (**3.24**), butylamine, DCE and acetonitrile, it was determined that a reaction between the amine and one of the solvents was taking place. This was confirmed by irradiation of butylamine or morpholine in a mixture of acetonitrile/DCE 1:1; each experiment showed a reaction was taking place. This was more noticeable in the morpholine ^1H NMR spectrum as significant changes in chemical shifts were observed for the reacted morpholine compared with unreacted morpholine. Whereas with butylamine, there was considerable overlap

in the chemical shifts of reacted butylamine and unreacted butylamine, which led to the initial observation of the presence of butyl resonance. It seemed unlikely that a reaction would occur between the amine and acetonitrile and so it was deduced that a reaction maybe taking place with DCE. This was confirmed by the irradiation of morpholine in several solvents, DCE, acetonitrile and THF, morpholine was chosen as the proton NMR could be easily interpreted. In THF and acetonitrile no reaction was observed with recovery of the starting material. In the reaction with DCE, four new triplets appeared in the proton NMR spectrum, from this it was deduced that substitution of one of the chlorine atom on the DCE with morpholine was occurring to give **3.32** (Figure 3.37).

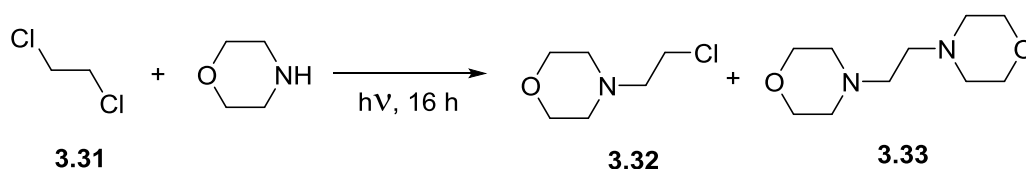


Figure 3.37: Proposed reaction

It is thought that only one chlorine is undergoing substitution as 4 triplets appear in the proton NMR spectrum. If both chlorines had been substituted, the product would be a symmetrical molecule (**3.33**) which would result in 3 peaks in the proton NMR spectrum, two triplets for the morpholine and a singlet for the central ethyl. As there is a large excess of DCE in comparison with the morpholine, it is logical that there is only one substitution per DCE molecule as the number of unreacted DCE molecule would greatly out number that of the reacted ones.

Due to this development it has been determined that DCE is not a suitable solvent for use in the catalytic cycle when photolysis is being used. As the side reaction would lead to consumption of any amine used and a greater excess may be needed, thus lowering the atom efficiency of a reaction. As THF has given good results for many of the reactions tried, it is thought this will be a good alternative.

As mentioned previously, the reactions which have been carried out were to determine the feasibility of the project. Due to the problem encountered with finding conditions for the exchange of the arene species on the sandwich complex, a full catalytic cycle was not developed. Therefore very few of the compounds were

fully isolated, as they were not the intended product for the work. As it was decided to not carry on with this project, the side reactions were not further explored.

3.4 Conclusion

In conclusion, the activation of styrene towards nucleophilic attack through η^6 -binding to ruthenium in $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$ has been achieved, with sole addition at the terminal carbon of the alkene, to give the anti-Markovnikov product. It was found that cyclic secondary amines gave complete conversion, whereas the use of acyclic secondary amines resulted in little or no conversion. Primary amines were observed to give moderate conversions, but a higher temperature was needed compared with cyclic secondary amines. Alcohols have so far proved unreactive, even at higher temperatures. Dimethyl malonate was found to react when activated with sodium methoxide, although some decarboxylation was observed.

It was demonstrated that a Diels–Alder reaction could also be achieved with styrene activated by $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$, and moderate to good conversions have been achieved with 1,2,3,4,5-pentamethylcyclopentadiene.

An $\text{S}_{\text{N}}\text{Ar}$ reaction has also been shown to occur with an activated aryl chloride and an amine at 80 °C, as has been previously reported. This reaction has also been shown between $[\text{RuCp}(\eta^6\text{-4-chlorotoluene})]\text{PF}_6$ and dimethyl malonate.

Arene exchange has been achieved for $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$ in up to a 69% conversion using a combination of heat and irradiation using a 400 W medium pressure mercury lamp, but exchange of $[\text{RuCp}(\eta^6\text{-N-methylaniline})]\text{PF}_6$ proved unsuccessful, therefore suggesting this method is not viable for developing a catalytic cycle. Through investigation of the catalytic cycle it has been found that free styrene undergoes nucleophilic addition with an amine when the reaction is irradiated, without the need for activation of the styrene with the ruthenium catalyst. It was also found that activated $[\text{RuCp}(\eta^6\text{-4-chlorotoluene})]\text{PF}_6$ undergoes $\text{S}_{\text{N}}\text{Ar}$ reaction with butylamine with irradiation alone, although a higher conversion is seen when both irradiation and heat is used. Finally, a reaction was shown to take place between DCE and amines when exposed to irradiation.

3.5 Future Work

There is still much scope to be explored in this research area, although the nucleophilic addition reaction had been optimised for secondary amines, there is still room for improvement for the primary amine reaction and the scope of the reaction with malonates has yet to be explored. A limiting factor of the reaction with malonates is their need to be activated in the reaction. Currently, an alkoxide has been used to do this; which may be problematic as the corresponding alkoxides for each malonate may be needed to prevent scrambling of the product through transesterification of the starting material.

Further optimisation of the Diels–Alder with styrene reaction and exploration of the scope of the reaction is needed, as 1,2,3,4,5-pentamethylcyclopentadiene has only been used as diene so far.

Development of the S_NAr reaction is required, where a universal set of reaction conditions can be used for a broad scope of substrates. As these reactions are already known to work, it would be rational to have a robust catalytic cycle before focusing on the S_NAr reaction.

In all of the examples above the reactions have only been carried out using simple arenes such as styrene and 4-chlorotoluene. The use of substituted arenes, either on the ring or in the case of styrene on the ethylene group could be further explored. This will be more feasible when the arene exchange has been optimised, as this will lead to the easy addition of any arene to $[RuCp]PF_6$ from $[RuCp(\eta^6\text{-benzene})]PF_6$, without the need to use unstable $[RuCp(MeCN)_3]PF_6$.

As photocatalysis is not feasible for the styrene reactions due to the polymerisation of the styrene, other methods of arene exchange could be explored in the hope that an alternative catalytic route can be developed. As the sandwich complexes are relatively stable, this could be achieved by looking at alternative ligands to replace the Cp ligand, to afford less stable complexes, where the exchange can take place without the need for irradiation.

Exploration of the side reactions which were observed after irradiation, to further understand these reactions and either find a way to prevent them or developing them as reaction in their own right would also be of interest.

Our initial attempt focused on ruthenium, as it is NMR inactive, meaning quick and easy analysis of the complexes could be carried out. Finally the investigation of using more abundant metals, such as iron, instead of ruthenium could be explored. As was mentioned in the introduction, iron has similar reactivity in this type of chemistry and therefore could behave in a similar manner to ruthenium in these reactions. As iron is a more abundant metal in comparison to ruthenium, the use of iron as a catalyst is far more sustainable.

4 Urea catalysed S_NAr reactions of 1-chloro-4-nitrobenzene

4.1 Introduction

It is known that the electron withdrawing character of a nitro group when present on an aromatic ring can activate the ring towards S_NAr reaction, as mentioned in Chapter 1.

There are many examples of ureas and thioureas being used to further activate nitro groups in reactions of aliphatic systems, but no examples of enhanced activity in aromatic systems. Many of the literature examples of organocatalysis using (thio)ureas involves bifunctional ureas to catalyse enantioselective and diastereoselective reactions.

One of the earliest reports of urea hydrogen bonding with a nitro group was by Etter *et al.* in 1990. The report discusses the hydrogen bonding of diarylureas with a variety of functional groups, such as nitro groups, carbonyls and ethers, demonstrating that a number of different bonding patterns can be observed through the cocrystallisation of different guest molecules with diarylureas.¹⁰⁸

Okino, Hoashi and Takemoto demonstrated the effectiveness of a thiourea in an enantioselective Michael reaction. The thiourea shown in **Figure 4.1** was found to give the best results after screening of thioureas with different aryl groups and functionalities on the amine. They found that the interaction of the nitro group with thioureas enhanced the electrophilicity of the nitroolefin to a subsequent Michael reaction. Investigation of the substrate scope determined that the reaction proceeds with different functionalities in the R^1 , R^2 and R^3 positions, although extended reaction times were needed in some cases. Good to excellent yields were obtained with high levels of *ee* observed in many cases.¹⁰⁹

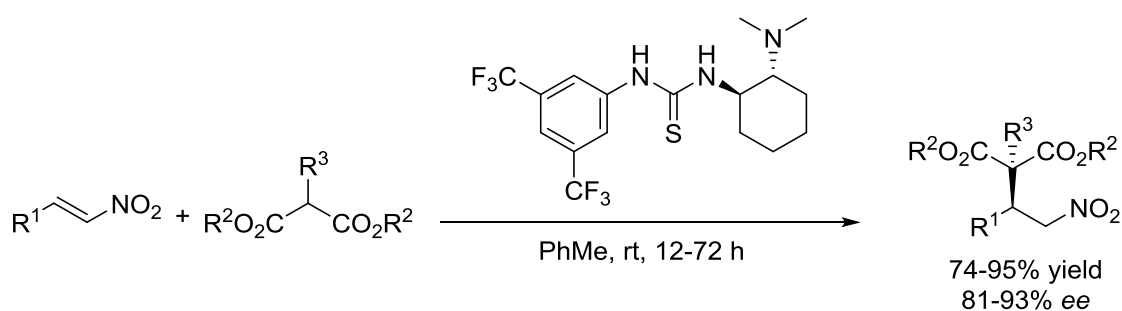


Figure 4.1: Enantioselective Michael reaction

They furthered this research by investigating the structure-activity relationship of the thiourea catalyst in the Michael reaction and proposing a possible mechanism. A series of thiourea and urea derivatives was synthesised to investigate how different functionality affected catalytic activity. It was found that the original bifunctional thiourea shown in **Figure 4.1** was the best catalyst. Using β -nitrostyrene, a more extensive malonate substrate scope study was carried out; excellent yields (74-99%) were obtained in many cases along with good to excellent *ee*'s (81-95%). It was also demonstrated that the thiourea catalysed the Michael addition between β -nitrostyrene and a series of ketoesters in 0.5 to 48 h at $-60\text{ }^{\circ}\text{C}$ to room temperature with excellent enantioselectivities and yields (**Figure 4.2**).¹¹⁰

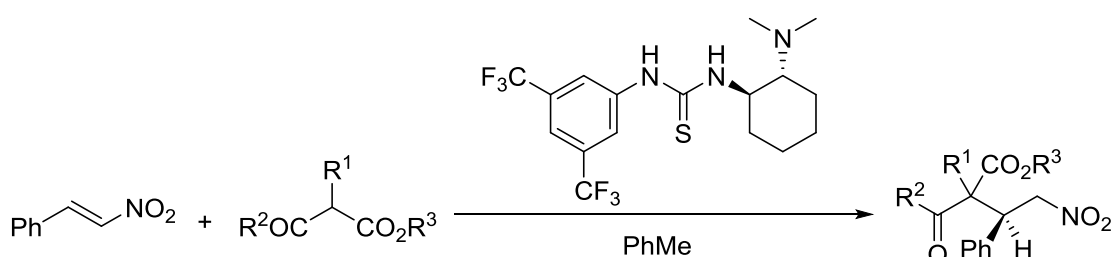


Figure 4.2: Michael reactions of ketoesters

Okino and others also demonstrated that the same catalyst could be used in an enantioselective Aza-Henry reaction. It was found that the asymmetric bifunctional thiourea catalysed the reaction between *N*-phosphinoylimine and nitromethane (**Figure 4.3**). Good yields of up to 91% were obtained for a range of arylimines, with moderate enantioselectivities between 63% and 76%. The reaction was also attempted with nitroethane, where a yield of 83% and *ee* of 67% was obtained, but no other nitro compounds were explored.¹¹¹

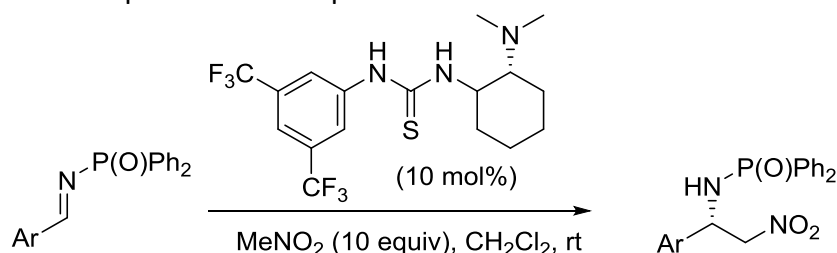


Figure 4.3: Organocatalysed Aza-Henry reaction

Yalalov *et al.* reported the organocatalysed Michael reaction between aromatic nitroolefins and acetone. Their initial report demonstrated the use of thiourea **4.1** as catalyst in the addition of acetone to β -nitrostyrene with 55% yield and 87% *ee*

(**Figure 4.4**).¹¹² Thiourea **4.2** was then developed as it was thought that removing the imidazolyl group may increase the efficiency of the catalyst, as the amine may reversibly form an enamine from a ketone, which could then act as an electrophile in the reaction. After optimisation of the reaction conditions catalyst **4.2** was shown to work with several aromatic nitroolefins in very good yields and *ee*'s.¹¹³



Figure 4.4: Yalalov's thioureas organocatalysts

Teng *et al.* reported the highly selective asymmetric nitro-Mannich reaction, with selectivity towards *anti*-addition. Initial optimisation of the reaction between boc-protected aldimine and nitromethane found conditions which gave the anti-product in high yield (85-99%) and 99% *ee* (**Figure 4.5**). These conditions were shown to tolerate electron withdrawing and donating groups on the ring of the aldimine. The scope of the nitroalkane was also explored, where it was found that along with excellent yields and enantioselectivities, the reaction was highly selective towards the *anti*-diastereomer.¹¹⁴

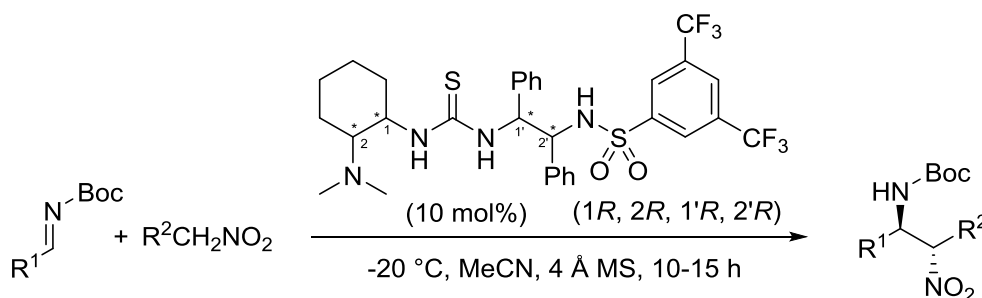


Figure 4.5: *Anti*-selective nitro-Mannich reaction

It was reported by Han and others that a highly selective nitro-Mannich reaction of α -substituted nitroacetates can be catalysed by bifunctional ureas (**Figure 4.6**). A series of substituted ureas and thioureas was investigated, the thiourea shown in **Figure 4.6** was most effective. After optimisation, the reaction could tolerate small aliphatic groups as the R^1 substituent and a series of aromatic substituents in the R^2 position, with very good yields, excellent *ee*'s and good diastereoselectivity.¹¹⁵

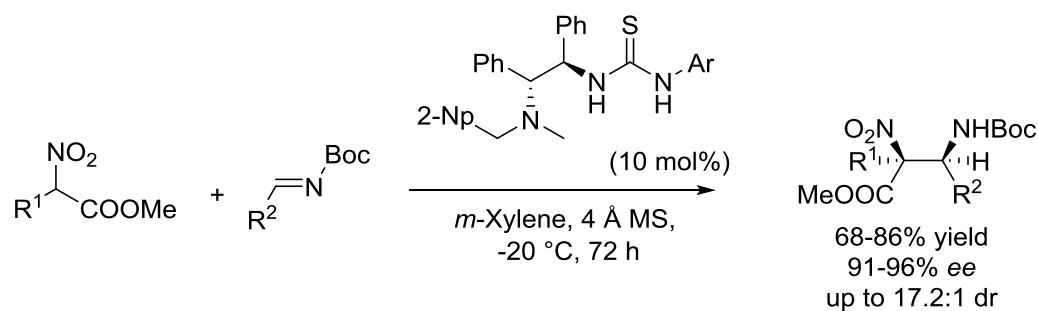


Figure 4.6: Han and others nitro-Mannich reaction

Jiang *et al.* reported the stereocontrolled conjugated addition of heterocycle-bearing ketones with nitroalkenes *via* organocatalysis, to afford nitro heteroaromatic ketones which can then be further transformed into carboxylic acid bearing pyrrolidines (**Figure 4.7**).¹¹⁶

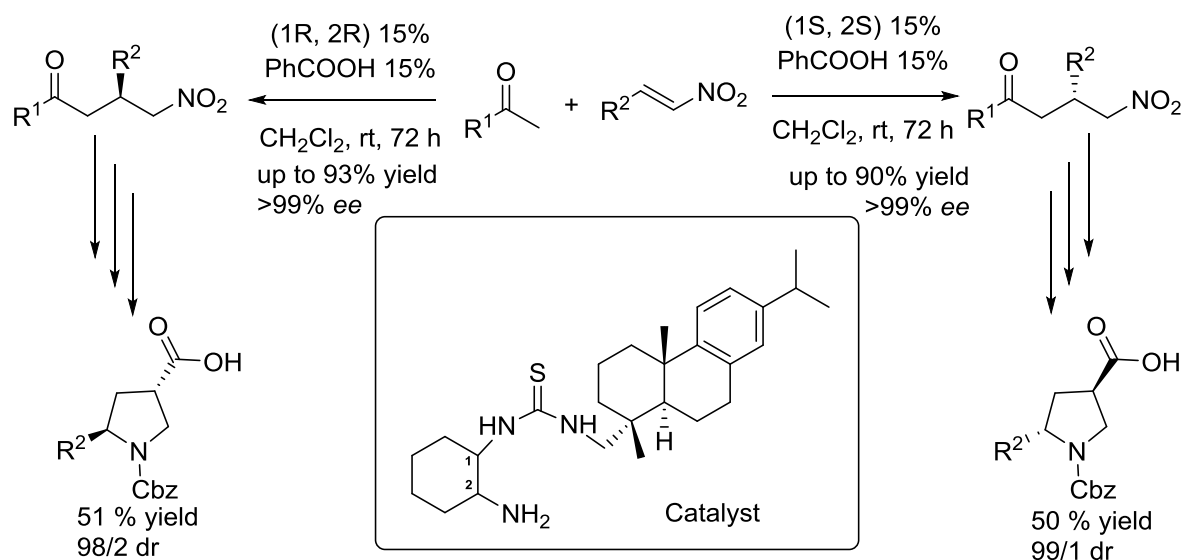


Figure 4.7: Enantioselective Michael addition

The addition of thioacetic acid to nitroalkenes was reported by Kimmel and others (**Figure 4.8**). A series of sulfinylureas was investigated and compared to Takemoto's catalysts,¹¹⁰ finding their own catalysts gave better selectivities. Using the optimised conditions it was demonstrated that aromatic and aliphatic nitroalkenes could be tolerated in good to moderates yields of 63% to 95%, and high enantioselectivities of 80% to 91%.¹¹⁷

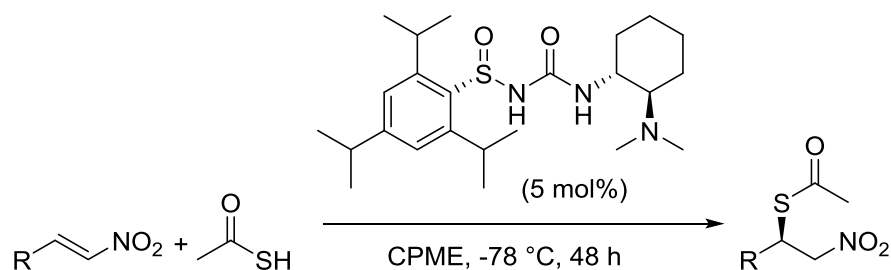


Figure 4.8: Addition of thioacetic acid to nitroalkenes

This work was then furthered by carrying out the addition on α,β -disubstituted nitroalkenes in a cyclic system to introduce two stereocentres. Excellent yields (up to 98%), enantioselectivities (up to 94%) and diastereoselectivities (up to 99:1) were obtained in most examples given. Through structure-activity relationship studies they were able to show that the sulfinyl group plays a key role in the enantioselectivity of the catalyst.¹¹⁸

Kimmel also reported the success of another similar sulfinyl urea catalyst in the addition of Meldrum's acid derivatives to nitroalkenes in highly enantioselective and diastereoselective reactions (**Figure 4.9**). The reaction tolerated electron rich and poor aromatics in the R position along with aliphatic examples. α,β -Disubstituted nitroalkenes were also demonstrated to be compatible with the reaction conditions, with small groups in the α -position and cyclic systems.¹¹⁹

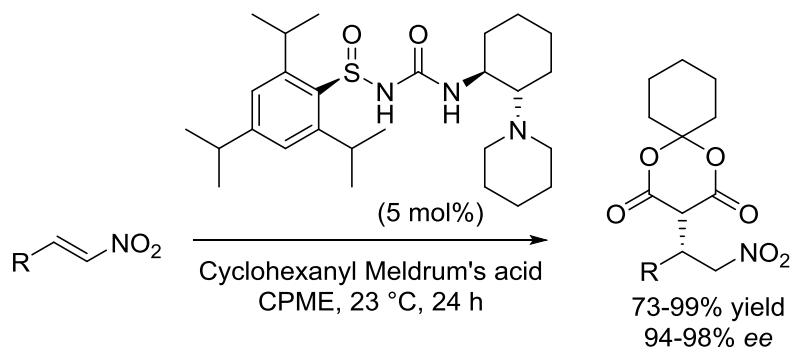


Figure 4.9: Addition of Meldrum's acid to nitroalkenes

In 2010 Cao and others reported the asymmetric Michael addition of ketones to esters catalysed by pyrrolidine-ureas (**Figure 4.10**). Once optimised, it was demonstrated that cyclohexanone reacted smoothly with various nitroolefins with high enantio- and diastereoselectivities (83-96%, 50:1). Nitrostyrene was also shown to react with a series of ketones and aldehydes with moderate enantioselectivities and diastereoselectivities where applicable.¹²⁰

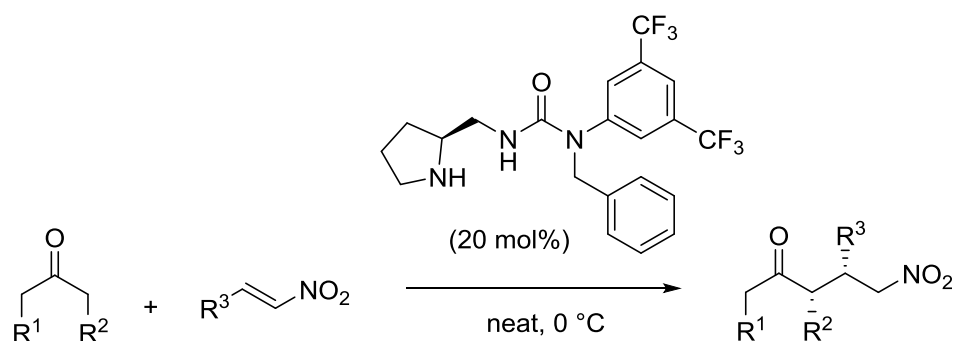
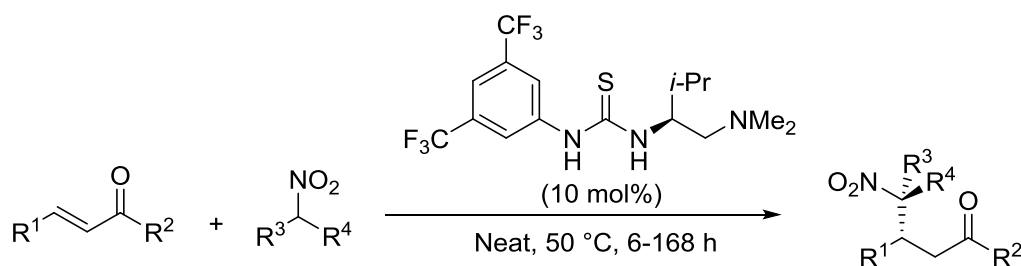


Figure 4.10: Asymmetric addition of ketone to nitroalkene

Manzano *et al.* reported the use of bifunctional ureas in the catalysis of a Michael addition between a nitroalkane and an α,β -unsaturated ketone (**Figure 4.11**). Upon optimisation the substrates were explored, a wide range of functional groups were used with yields varying from 0 to 100%, although in many cases reaction times as long as 168 hours were needed to gain moderate yields. Although poor yields were obtained in some instances, the *e.r.* in many cases was very good. With nitromethane as the nitroalkane, a small substituent in the R^2 position, such as a methyl group, gave an almost racemic mixture, whereas a larger phenyl group gave better selectivity (up to 95:5). With chalcone as the α,β -unsaturated ketone, aliphatic and ester groups were tolerated in the R^3 position. Very good yields (75-100%) and enantiomeric ratios (85:15-98:2) were reobtained, although near equimolar mixtures of diastereomers were obtained in some cases. Exploration of the mechanism through computational studies, suggested that the reaction proceeds through two interactions, one between the urea and the nitro group and one between the amine in its protonated form and the ketone.¹²¹

Figure 4.11: Michael addition of nitroalkane to α,β -unsaturated ketone

The Mattson group have published several reports on the use of a difluoroboronate urea (**Figure 4.12**).

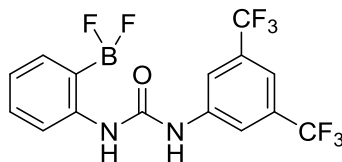


Figure 4.12: Difluoroboronate urea

So and Mattson demonstrated the use of this organocatalyst in a three component coupling between an α -nitro- α -diazo ester, an aniline species and a nucleophile (**Figure 4.13**). Electron rich and poor anilines were tolerated along with bulkier nucleophiles to give good to excellent yields.

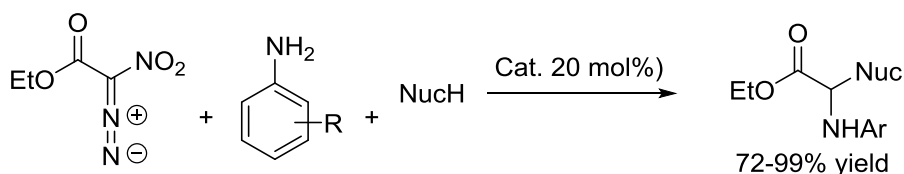


Figure 4.13: Three component coupling

The mechanism was explored experimentally and computationally, it is suggested the mechanism proceeds through a urea-stabilised nitrocarbene and a urea-facilitated stepwise N-H insertion is favoured. Direct N-addition of the aniline and loss of the NO_2^- leads to the protonated aminal, followed by proton transfer to afford the product (**Figure 4.14**).^{122,123}

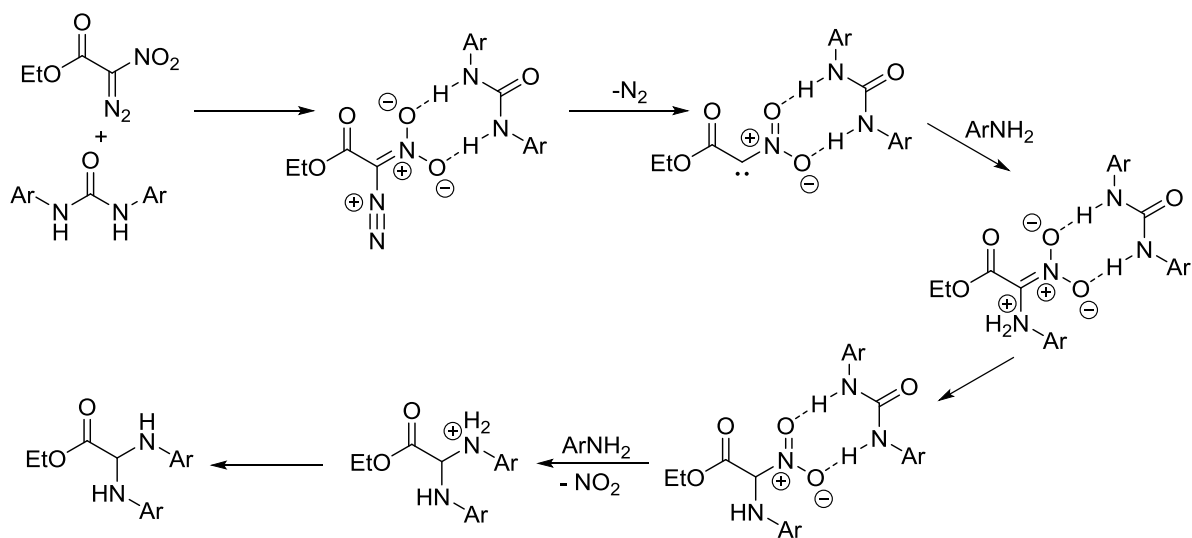


Figure 4.14: One possible route for urea catalysed three component reaction

The urea shown in **Figure 4.12** was also shown to promote the [3 + 3] cycloaddition between a nitrocyclopropane ring and a nitron to generate an oxazinane (**Figure 4.15**). R^1 was shown to tolerate a variety of *para*-substituted aryl groups with up to

99% yield, although the presence of substituents in the *ortho* position on the ring gave a reduction in yield (41%), an allyl group was also shown to be tolerated but a yield of only 23% was obtained. Moderate to excellent yields of between 47% to 99% were also obtained for various electron rich and poor aromatic groups in the R² position. The R³ position was not fully explored with most examples having a phenyl group apart from one with a benzyl group present, a reduction in yield was observed in this case.¹²⁴

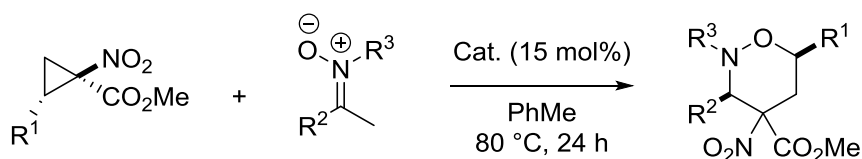


Figure 4.15: [3+3] cycloaddition

Kawazoe and others reported the Michael addition of thiols to β -nitrostyrene catalysed by a symmetric urea. A series of symmetric and asymmetric ureas and thioureas was synthesised and their activity investigated in the target reaction. A bulky symmetric urea was found to give the best enantioselectivity and moderate yields, and this was used to further optimise the reaction (**Figure 4.16**). Very good yields were obtained for various electron rich and poor aromatic groups on the β -nitrostyrene, as well as the bulky naphthyl group and aliphatic groups, although poor enantioselectivity was observed for the latter two examples.¹²⁵

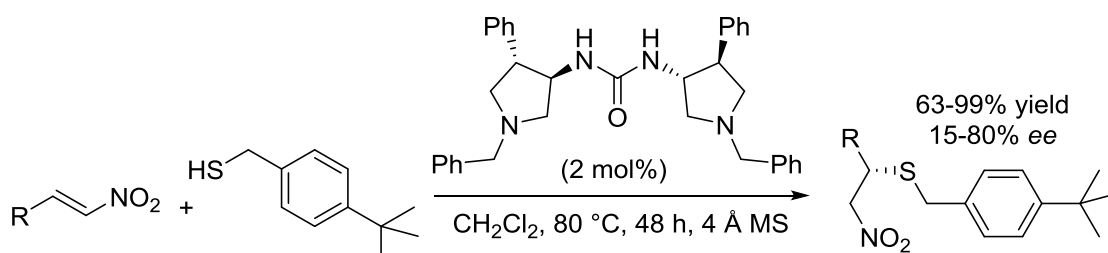


Figure 4.16: Michael addition of thiols

As well as urea derivatives acting as organocatalysts through H-bonding with nitro groups, they can also act as catalysts through H-bonding with other groups such as carbonyls, nitrones and sulfoxides.

In 1995 Curran and Kuo reported the acceleration of a Claisen rearrangement and an improvement in the stereoselectivity of a radical allylation of sulfoxides catalysed by the same urea (**Figure 4.17**).^{126,127}

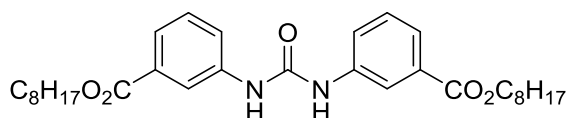


Figure 4.17: Curran and Kuo's urea

Okino et al. reported the addition of trimethylsilyl cyanide (TMSCN) to nitrones catalysed by a thiourea catalyst. The reaction between TMSCN and nitrones was shown to work for cyclic and acyclic nitrones, and was selective for the alkene adjacent to the nitron when more than one alkene was present (**Figure 4.18**).¹²⁸

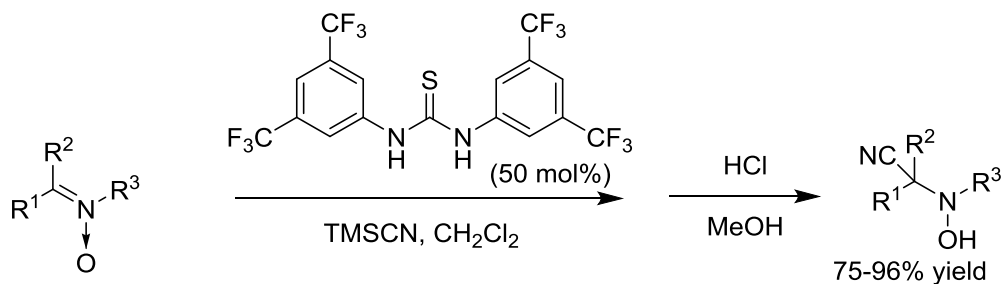


Figure 4.18: Addition of cyano group to nitron

They also demonstrated that the thiourea catalysed the reaction between nitrones and ketene silyl acetals to give 1,2-isoxazolidin-5-ones (**Figure 4.19**). Both cyclic and acyclic nitrones were tolerated, along with small groups on the ketene silyl acetals. It was also demonstrated that the catalyst could catalyse a reaction between an aromatic aldehyde and ketene silyl acetals.¹²⁸

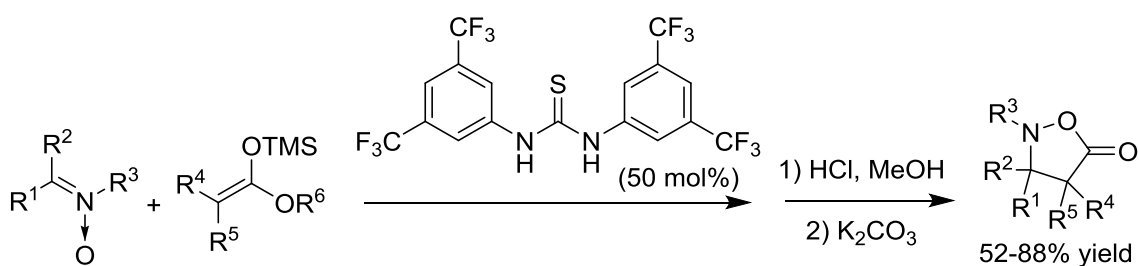


Figure 4.19: Formation of 1,2-isoxazolidin-5-ones

Wenzel and Jacobsen reported the thiourea catalysed asymmetric Mannich reaction to synthesise β -aryl- β -amino acids (**Figure 4.20**). A urea catalyst was investigated, and although a conversion of 92% was achieved, a disappointing *ee* of only 47% was observed. Modification of the catalyst to a thiourea and optimisation of the conditions resulted in improvement, with yields up to 99% and enantioselectivity of 86-98%. The reaction was demonstrated to tolerate aromatic groups in the R position.¹²⁹

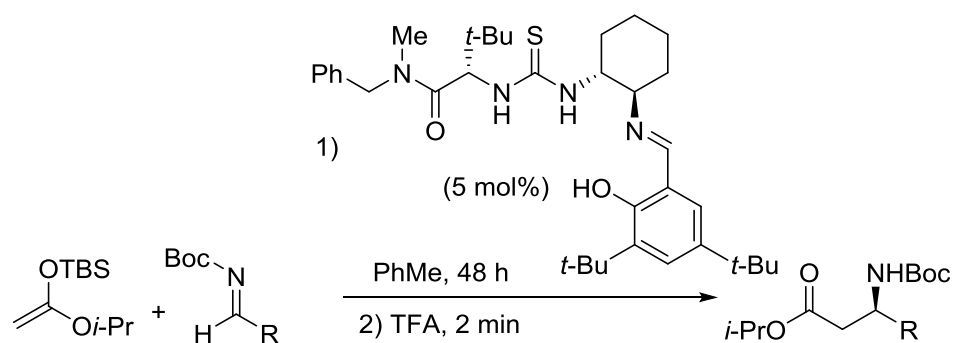


Figure 4.20: Thiourea catalysed Mannich reaction

Hrdina and others reported the use of a thiourea catalyst in combination with a silane precursor catalyst to facilitate the rearrangement of epoxides to aldehydes. A series of silane precursors and ureas and thioureas was screened, the combination shown in **Figure 4.21** gave the greatest yield by far. Various aliphatic groups gave good to excellent yields when Ar was a phenyl group. When larger aromatic groups were investigated, a decrease in yield was observed. The proposed mechanism shows a concerted ring opening of the epoxide and migration of R^2 to form the aldehyde and the tertiary centre.¹³⁰

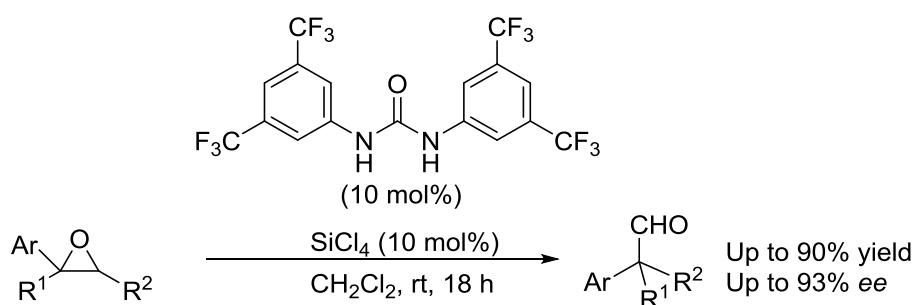
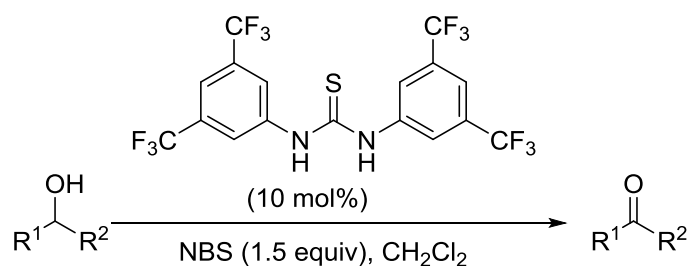


Figure 4.21: Epoxide rearrangement

The thiourea catalysed oxidation of alcohols to ketones facilitated by *N*-bromosuccinimide (NBS) was reported by Tripathy and Mukherjee. A series of ureas, thioureas, carbamates and thiocarbamates was screened as catalysts, the sulfur containing molecules performed considerably better than those containing oxygen. Although several of the catalysts performed equally well, the thiourea shown in **Figure 4.22** was chosen due to the ease of accessibility. Moderate to good yields of 51 to 92% were obtained for a series of aromatic and cyclic alcohols, although reaction temperatures and time varied considerably, with reactions taking up to 90 hours.¹³¹

Figure 4.22: *N*-Bromosuccinimide-mediated oxidation of alcohols

Couch *et al.* reported the urea catalysed insertion reaction of sulfur and oxygen nucleophiles, into a C=N bond of α -aryldiazoacetates, resulting in the release of N₂ (**Figure 4.23**). The incorporation of the difluoroboronate into the urea, resulted in a considerable increase in conversion when compared with the ureas without the boronate. Yields of 42 to 93% were gained for various S and O nucleophiles, functionalities on the α -aryldiazoacetate were also tolerated.¹³²

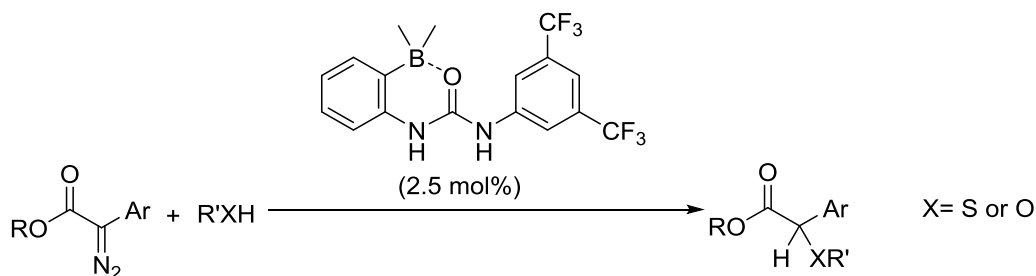


Figure 4.23: Urea catalysed insertion reaction

As discussed, there are many examples of urea and thiourea catalysis with aliphatic systems, activating molecules through various functional groups and covering a wide range of reactions, but there are no examples of urea activating an aromatic ring though H-bonding to a nitro group. Therefore the possibility of activating a halonitroarene for an S_NAr reaction was explored.

4.2 Aim and objectives

Urea is known to activate nitro containing aliphatic molecules, enhancing their reactivity, through forming hydrogen bonds with the oxygens on the nitro group. We hypothesise that the electron withdrawing character of the nitro group on an arene can be enhanced in a similar manner through hydrogen bonding with a urea analogue. This enhanced electron withdrawing character will further activate the arene and make it more susceptible to S_NAr reactions (**Figure 4.24**). It is envisioned that simple reaction conditions will be needed due to the stability of the reagents used, leading to the development of an inexpensive catalytic system.

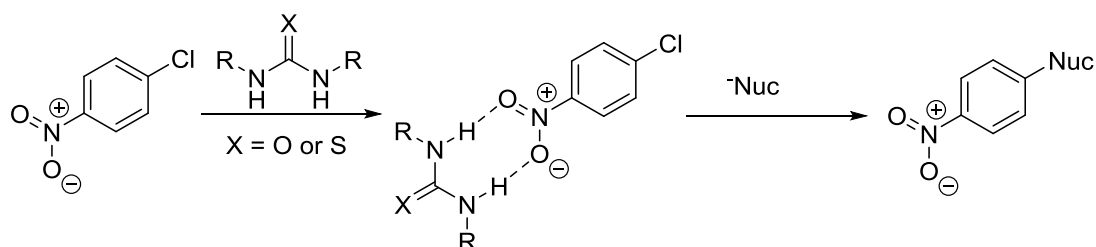


Figure 4.24: Proposed activation of nitroarenes

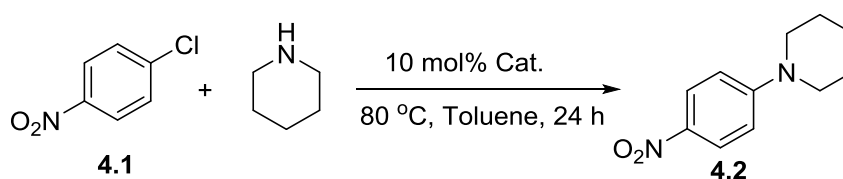
4.3 Results and discussion

As mentioned in the introduction the activation of nitro groups through hydrogen bonding with (thio)ureas to enhance the electron withdrawing ability of the nitro group in aliphatic systems has been explored within the literature. Alternatively the use of this interaction to activate aromatic systems has not been explored, which led to our interest in the area.

4.3.1 Catalyst screen

An initial screening reaction of several ureas and thioureas demonstrated that there was the potential to develop a catalytic system to promote the S_NAr reaction with 1-chloro-4-nitrobenzene using a urea as an organocatalyst. To develop a system that could be easily reproducible, if possible it was desirable to find a catalyst that was simple and commercially available.

Table 4.1: (Thio)urea screen



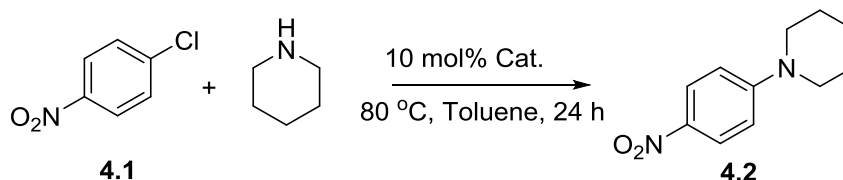
Entry	Compound	Urea	Conversion (%) ^[a]
1	-	Background	8
2	4.3	1,3-Diisopropylthiourea	12
3	4.4	<i>N,N'</i> -Diphenylthiourea	11
4	4.5	<i>N,N'</i> -Dimethylurea	20
5	4.6	1,3-Diphenylurea	18
6	4.7	Urea	9

1-Chloro-4-nitrobenzene (1 mmol), piperidine (1.5 mmol) and catalyst (0.1 mmol) in toluene at 80 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

Taking ureas and thioureas with varying sized substituents showed that *N,N'*-dimethylurea (**4.5**) gave an enhancement with a conversion of 20% (Table 4.1, entry 4) compared with the background conversion of only 8% (Table 4.1, entry 1). 1,3-Diphenylurea (**4.6**) also showed some improvement with a conversion of 18% (Table 4.1, entry 5). 1,3-Diisopropylthiourea (**4.3**) and *N,N'*-diphenylthiourea (**4.4**)

demonstrated a slight enhancement of 12% and 11% (**Table 4.1**, entry 2 and 3), respectively and unsubstituted urea (**4.7**) showed no activity above the background rate (**Table 4.1**, entry 6). For this reason it was decided to investigate further the catalytic activity of *N,N'*-dimethylurea and 1,3-diphenylurea.

Table 4.2: Increasing equivalents of urea



Entry	Urea (Equiv)	1,3-Diphenylurea Conversion (%) ^[a]	<i>N,N'</i> -Dimethylurea Conversion (%) ^[a]
1	0	8	8
2	0.05	16	16
3	0.1	20	19
4	0.2	22	31
5	0.5	19	42

1-Chloro-4-nitrobenzene (1 mmol), piperidine (1.5 mmol) and catalyst (0.1 mmol) in toluene at 80 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

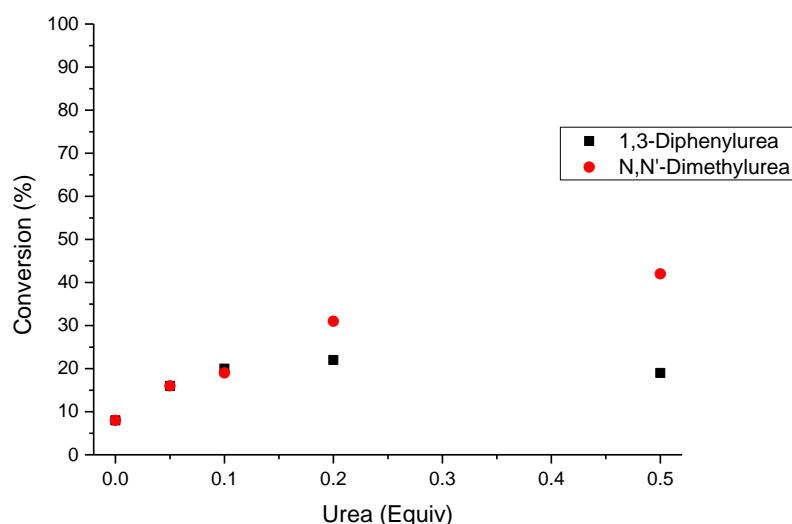


Figure 4.25: Increasing equivalents of urea

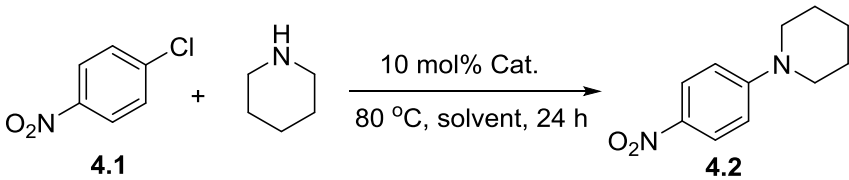
To determine the feasibility of the project a screen was carried out with increasing amounts of urea to determine its effect on the conversion. As can be seen from **Table 4.2** increasing the amount of *N,N'*-dimethylurea from none to 0.5 equivalents

in comparison with 1-chloro-4-nitrobenzene, increases the conversion from a background rate of 8% to 42% (**Figure 4.25**). In the case of 1,3-diphenylurea, although there is an initial increase in conversion up to 0.2 equivalents, this is seen to drop off at 0.5 equivalents. It is thought this may be due to insolubility of the diphenylurea, forming a thick paste at higher concentrations which may lead to problems with mixing within the reaction mixture.

4.3.2 Solvent screen

Various solvents of different natures were explored, to find the most compatible for our S_NAr reaction.

Table 4.3: Solvent screen



Reaction scheme: 1-chloro-4-nitrobenzene (4.1) + piperidine $\xrightarrow[80\text{ }^{\circ}\text{C, solvent, 24 h}]{10\text{ mol\% Cat.}}$ 1-(4-nitrophenyl)piperidine (4.2)

Entry	Solvent	Conversion ^[a] (%) 1,3-Diphenylurea	Conversion ^[a] (%) <i>N,N'</i> -Dimethylurea	Conversion ^[a] (%) Background
1	Toluene	16	23	10
2	DCE	1	2	2
3	Hexane	22	35	13
4	THF	42	37	34
5	Ethanol	40	36	34
6	Cyclohexane	11	32	11
7	IPA	33	34	24
8	Ethyl acetate	30	36	23
9	Water	27	14	10
10	Octane	12	34	9
11	2-Pentanol	36	33	31

1-Chloro-4-nitrobenzene (1 mmol), piperidine (1.5 mmol) and catalyst at 80 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

Various solvents were screened to determine if a better system than toluene (**Table 4.3**, entry 1) could be found. DCE and water proved ineffective in the reaction (**Table 4.3**, entry 2 and 9), although alcohols, ethanol, IPA and 2-pentanol gave moderate conversions (**Table 4.3**, entry 5, 7 and 11), they did not promote the

catalytic activation of the urea. Hexane and cyclohexane gave similar results (**Table 4.3**, entry 3 and 6), the lower boiling point of hexane means it limits exploration of optimum temperature for the reaction. Similarly ethyl acetate showed some enhancement (**Table 4.3**, entry 8), but the boiling point could be a limiting factor. THF gave the highest conversion (**Table 4.3**, entry 4) and octane gave good compatibility with *N,N'*-dimethylurea (**Table 4.3**, entry 10) and with a higher boiling point lacks the limitations of hexane. Therefore it was determined that THF, cyclohexane and octane would be further investigated as possible solvents.

At this point it was decided that as *N,N'*-dimethylurea was outperforming 1,3-diphenylurea and due to problems with solubility at higher concentrations, that further optimisation of the reaction would be carried out using *N,N'*-dimethylurea as the catalyst. *N,N'*-dimethylurea is also 8.9 times cheaper per mole than 1,3-diphenylurea. *N,N'*-dimethylurea costs £13.50 for 100 g and 1,3-diphenylurea costs £49.90 for 100g (prices taken from Fisher Scientific, <http://www.fisher.co.uk>, on the 13/08/2015), this equates to £11.95 and £106.17 per mole, respectively.

To determine which solvent was most compatible, experiments were carried out increasing the number of equivalents of *N,N'*-dimethylurea in each solvent. Although a catalytic loading of 0.1 was showing some enhancement of the reaction, it was decided to explore higher catalytic loading while investigating the solvent.

Although THF gave the best conversions at 0.1 equivalents (**Table 4.4**, entry 2), at higher concentrations of the urea little improvement is observed in the conversion, also due to its boiling point there are restrictions on further optimising the reaction with regard to temperature.

Table 4.4: Comparison of octane, cyclohexane and THF

Reaction scheme: 1-chloro-4-nitrobenzene (4.1) + pyrrolidine $\xrightarrow[80\text{ }^{\circ}\text{C, solvent, 24 h}]{N,N'\text{-Dimethylurea}}$ 1-(4-nitrophenyl)pyrrolidine (4.2)

Entry	Equivalents of <i>N,N'</i> -dimethylurea	Conversion ^[a] (%) Octane	Conversion ^[a] (%) Cyclohexane	Conversion ^[a] (%) THF
1	0	5	10	33
2	0.1	38	26	44
3	0.5	63	56	52
4	1.0	67	64	61
5	1.5	68	73	61
6	2.0	71	69	62

1-Chloro-4-nitrobenzene (1 mmol), piperidine (1.5 mmol) and *N,N'*-dimethylurea at 80 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

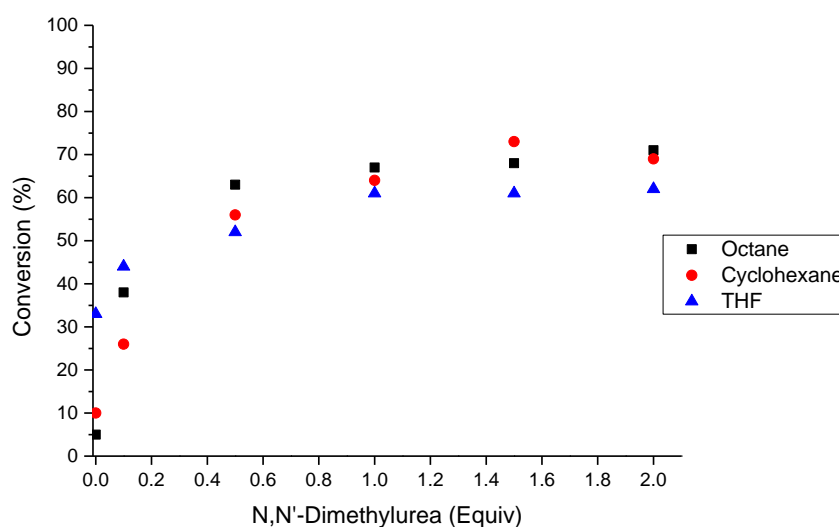


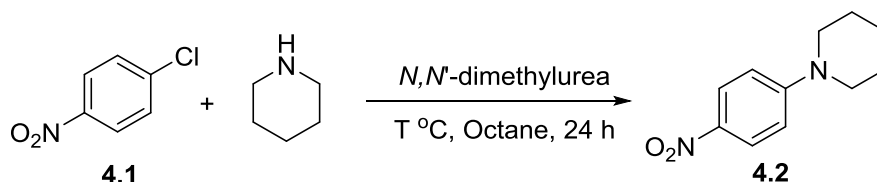
Figure 4.26: Comparison of octane, cyclohexane and THF

Generally using octane as the solvent gave the highest conversions, proving to be the best solvent when less than one equivalent of urea is used (Table 4.4, entry 4-6). The three solvents all show the same general trend at and above one equivalent of urea, only show slight improvements in conversion, suggesting there is little benefit of using over 0.5 equivalents of the catalyst. These trends can be seen in

Figure 4.26. From these results, octane was determined to be the sensible choice to continue with as the reaction solvent, its high boiling point of 126 °C also allows for a larger scope of possible reaction temperatures compared with THF and cyclohexane.

4.3.3 Temperature screen

Table 4.5: Temperature screen



Entry	<i>N,N'</i> -dimethylurea (Equiv)	Conversion ^[a] (%) 90 °C	Conversion ^[a] (%) 100 °C	Conversion ^[a] (%) 110 °C
1	0	17	20	21
2	0.1	45	56	52
3	0.2	55	59	56
4	0.4	64	65	66
5	0.6	67	65	68
6	0.8	67	70	69
7	1	69	72	68

1-Chloro-4-nitrobenzene (1 mmol), piperidine (1.5 mmol) and *N,N'*-dimethylurea at *T* °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

The effect of temperature of the reaction at varied catalyst loading was explored, with interesting results. In the background reaction increasing the temperature above 90 °C had little effect on the reaction and comparable conversions were obtained at 90, 100, and 110 °C (**Table 4.5**, entry 1). The greatest variation is seen at 0.1 equivalents of catalyst (**Table 4.5**, entry 2), as expected the conversion is seen to increase with increasing temperature up to 100 °C, over this temperature a small decrease in conversion is observed. Increasing the temperature has little effect on the conversion with catalyst loadings above 0.1 equivalents, as shown in **Figure 4.27**.

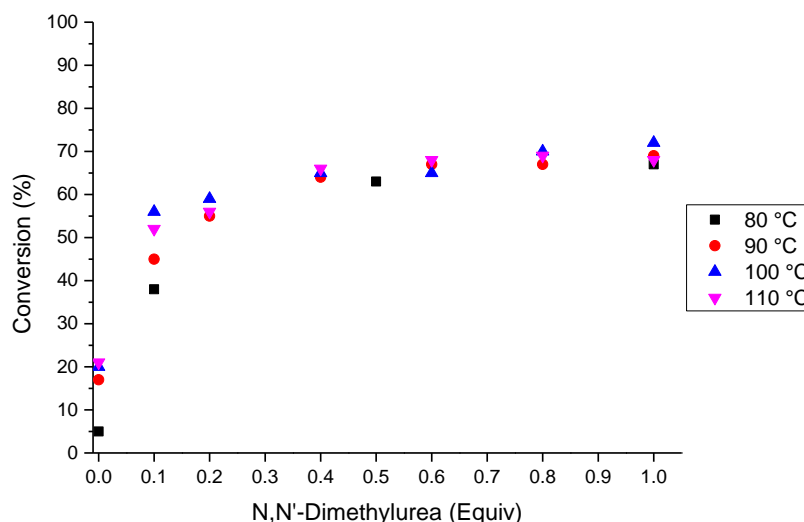


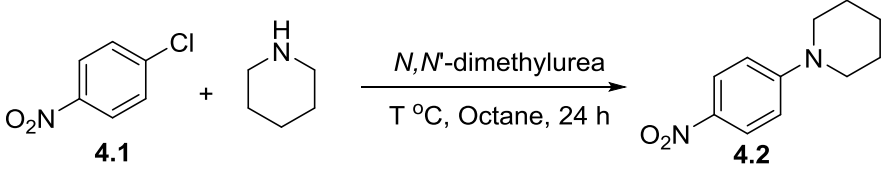
Figure 4.27: Temperature screen

This is unexpected as the same trend as that encountered for 0.1 equivalents was expected to be observed with increasing catalyst loading. This led us to believe that another factor may have been playing a role in limiting the conversion to around 70%. After some considerations, it was hypothesised that, as the side product of the reaction was HCl, this could possibly form a salt with the unreacted piperidine therefore removing its availability to react. This is supported by only obtaining conversions of up to 70%, roughly half of the 1.5 equivalents of piperidine, the HCl side product could then form the salt with the unreacted starting material rendering it unavailable to partake in the reaction.

4.3.4 Optimisation of equivalents of amine

To investigate this, the number equivalents of piperidine was increased to 2.5, greater than two equivalents was used so that when the reaction was reaching completion, there would still be an excess of piperidine present even if the salt was being formed.

Table 4.6: Exploration of equivalents of piperidine

						
Entry	<i>N,N'</i> -dimethylurea (equiv)	Conv. ^{[a][b]} (%) 80 °C	Conv. ^{[a][b]} (%) 90 °C	Conv. ^{[a][b]} (%) 100 °C	Conv. ^{[a][c]} (%) 90 °C	Conv. ^{[a][d]} (%) 90 °C
1	0	17	24	34	8	12
2	0.4	84	83	89	57	59
3	0.6	88	92	94	63	69

1-Chloro-4-nitrobenzene (1 mmol) and *N,N'*-dimethylurea at T °C for 24 h.^[a] Conversions determined by analysis of ¹H NMR spectra. ^[b] Piperidine (2.5 mmol) added. ^[c] Triethylamine (1.5 mmol) and piperidine (1.5 mmol) added. ^[d] Potassium carbonate (1.5 mmol) and piperidine (1.5 mmol) added.

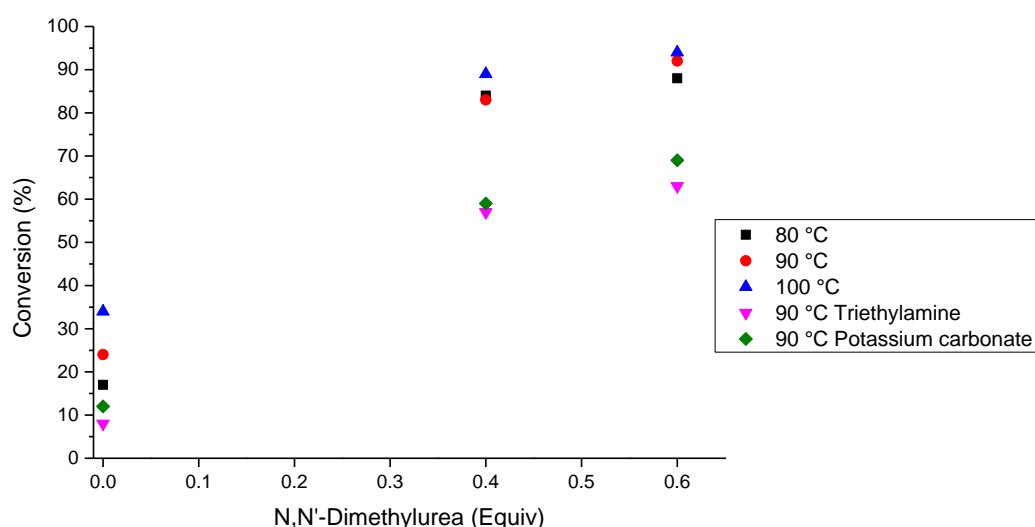


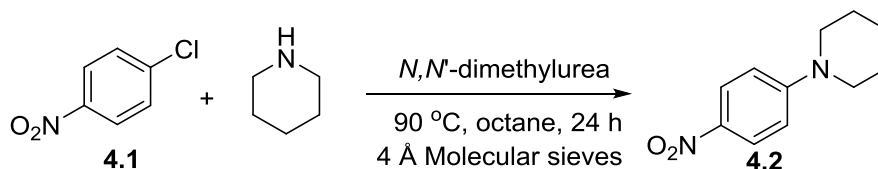
Figure 4.28: Exploration of equivalents of piperidine

As little improvement was seen with a catalyst loading above 0.6 equivalents it was decided to focus on catalyst loading of 0.4 and 0.6 equivalents. Similarly, a reduction of conversion was observed in temperatures above 100 °C, so we focused on exploring the reaction at 80, 90 and 100 °C. We were encouraged to observe that when the amount of piperidine was increased, the reaction proceeded to conversions above 70%, these results can be seen on **Figure 4.28**. With 0.4 equivalents of catalyst, similar conversions were observed at 80 and 90 °C, of 84% and 83%, respectively, with a slight increase at 100 °C with a conversion of 89%

(**Table 4.6**, entry 2). At catalytic loading of 0.6 equivalents, little difference was observed concerning the increase in temperature with conversions of 88%, 92% and 94% for 80, 90 and 100 °C, respectively (**Table 4.6**, entry 3). These results seemingly supported our theory that salt formation between unreacted piperidine and HCl was causing the reaction to stall at around 70% conversion. As it would not be desirable to use such a large excess of amine in all instances, especially if an expensive amine was used, it was thought a base additive could be used to remove the HCl byproduct from the reaction. This was investigated using triethylamine and potassium carbonate as additives and previous condition with 1.5 equivalents of piperidine at 90 °C. Disappointingly, with each of these additives, the conversions were similar to those achieved in the reaction without base additives, 67%, 63% and 69% for no base, triethylamine and potassium carbonate, respectively (**Table 4.6**, entry 3). As a slight decrease in conversion was observed in the case of triethylamine and a comparable conversion in the case of potassium carbonate, compared with no base present, the salt formation theory was not supported. It is still uncertain why with 1.5 equivalents of piperidine present, the reactions do not proceed past a conversion of 70%.

In another attempt to remove the HCl by product, 4 Å molecular sieves were added to the reaction; both powdered and beaded molecular sieves were investigated (**Table 4.7**). Beaded molecular sieves had little to no effect on the conversion of the reaction, whereas a slight increase was observed when powdered molecular sieves were added. But compared with the increase seen when the number of equivalents of piperidine was increased, this was only a small improvement and it was decided to focus on finding the optimum amount of piperidine in the optimisation process.

Table 4.7: Exploring the use of molecular sieves

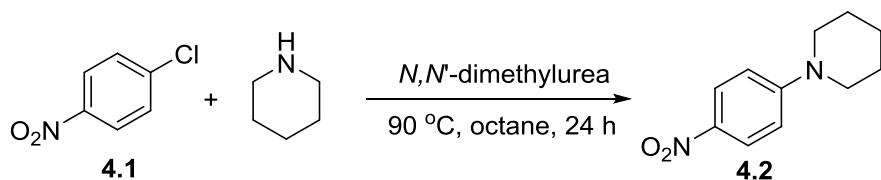


Entry	<i>N,N'</i> -Dimethylurea (Equiv)	Conversion ^[a] (%) Beaded MS	Conversion ^[a] (%) Powdered MS
1	0	20	10
2	0.4	62	68
3	0.6	66	72
4	0.8	66	74
5	1	72	74

1-Chloro-4-nitrobenzene (1 mmol), piperidine (1.5 mmol), 4 Å molecular sieves (100mg) and *N,N'*-dimethylurea at T °C for 24 h.^[a] Conversions determined by analysis of ¹H NMR spectra.

In attempt to push the reaction to completion the amount of piperidine in the reaction was investigated. The amount of piperidine with regard to 1-chloro-4-nitrobenzene was altered between 1.5 to 3 equivalents (**Table 4.8**).

Table 4.8: Equivalents of piperidine screen



Entry	<i>N,N'</i> -dimethylurea (equiv)	Conv. ^[a] (%) 2.0 equiv piperidine	Conv. ^[a] (%) 2.5 equiv piperidine	Conv. ^[a] (%) 3.0 equiv piperidine
1	0	15	24	28
2	0.2	60	77	85
3	0.4	78	91	97
4	0.6	78	91	99
5	0.8	85	94	99.5
6	1	83	93	99.5

1-Chloro-4-nitrobenzene (1 mmol), piperidine and *N,N'*-dimethylurea at 90 °C for 24 h.^[a] Conversions determined by analysis of ¹H NMR spectra.

As can be seen in **Figure 4.29** an improvement in conversion was observed for each half an equivalent added with 2 equivalents giving better results than 1.5 equivalents and so on. Pleasingly, with 3 equivalents of amine and a catalytic loading of between 0.4-0.6 equivalents of *N,N'*-dimethylurea, the conversion was quantitative.

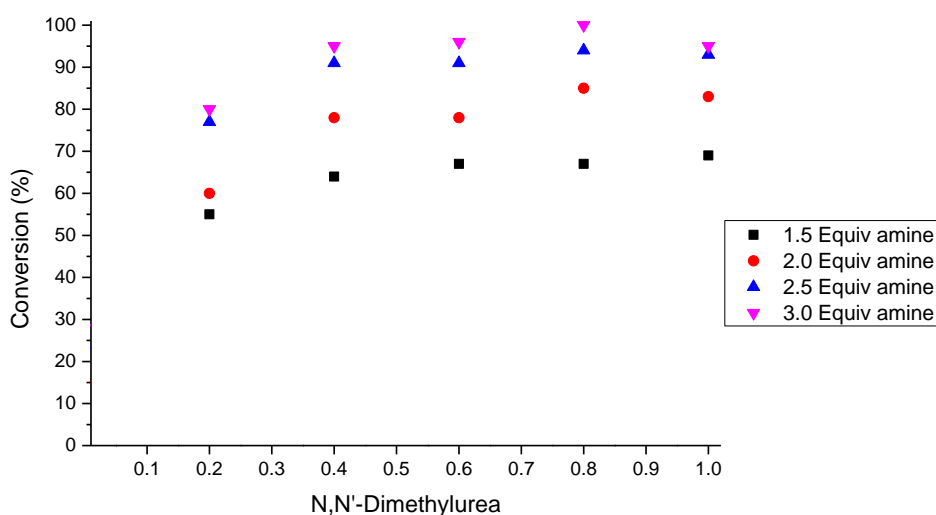


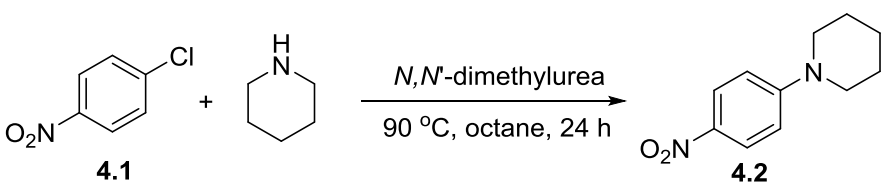
Figure 4.29: Equivalents of piperidine screen

4.3.5 Reaction profile

The conversion over time was monitored to determine if the full 24 hours was needed for the reaction to reach completion (**Table 4.9**).

Initially the increase in conversion is linear up to about 5 hours, the rate of increase then slows down as less starting material is available. After 16 hours the rate of reaction tapers off at about 90% conversion, taking another 6 hours for the reaction to near completion at 98%. This demonstrated that the full 24 hours is needed for quantitative conversions to be obtained (**Figure 4.30**).

Table 4.9: Time monitored reaction

			
Time (h)	Conversion ^[a] (%)	Time (h)	Conversion ^[a] (%)
1	11	17	93
2	23	18	93
3	36	19	93
4	46	20	93
5	52	21	94
6	59	22	98
7	68	23	99
8	71	24	99
16	91		

1-Chloro-4-nitrobenzene (1 mmol), piperidine (3 mmol) and *N,N'*-dimethylurea in octane at 90 °C for 24 h.^[a] Conversions determined by analysis of ¹H NMR spectra.

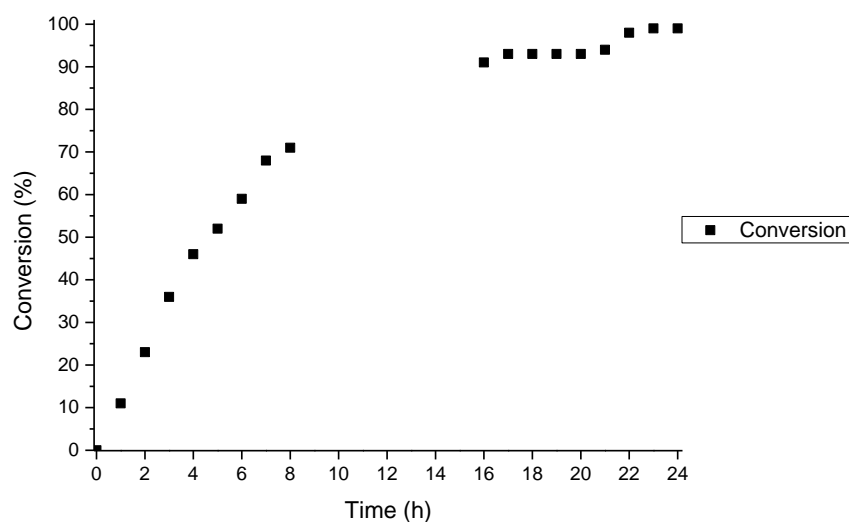


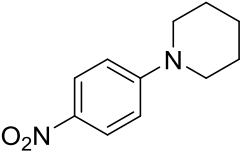
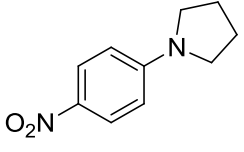
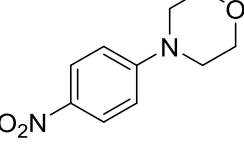
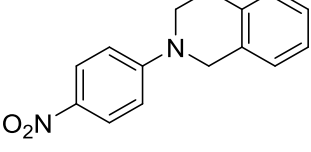
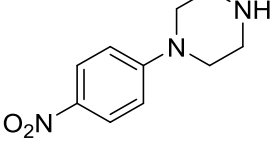
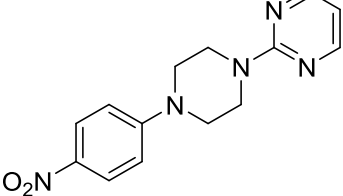
Figure 4.30: Time monitored reaction

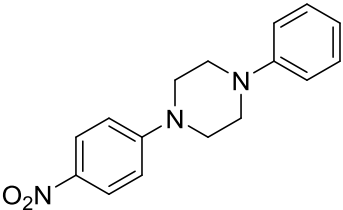
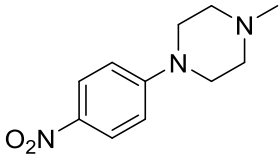
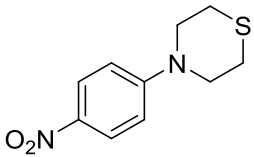
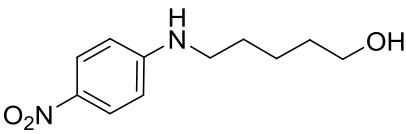
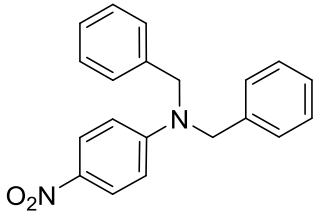
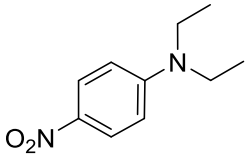
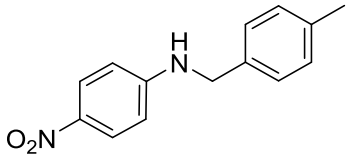
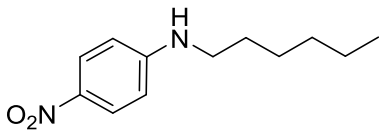
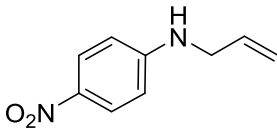
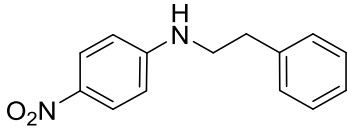
It was therefore decided that the condition moving forward towards the substrate scope would be 1 equivalent of 1-chloro-4-nitrobenzene, 3 equivalents of amine and 0.5 equivalents of *N,N'*-dimethylurea in octane at 90 °C for 24 hours.

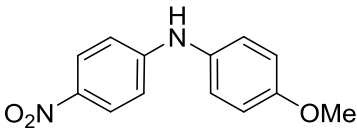
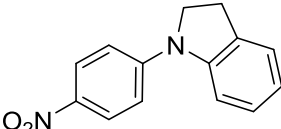
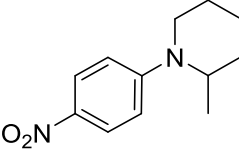
4.3.6 Substrate scope

Once optimised reaction conditions had been obtained, the scope of the amines which were tolerated in the reaction was investigated.

Table 4.10: Amine substrate scope

$ \text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{Cl} + \text{HNR}'\text{R}'' \xrightarrow[90\text{ }^\circ\text{C, octane, 24 h}]{N,N'\text{-dimethylurea (0.5 equiv)}} \text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{NR}'\text{R}'' $			
Entry	Compound	Product	Yield (%) (Conversion (%)) ^[a]
1	4.2		89
2	4.8		95
3	4.9		87
4	4.10		77
5	4.11		90
6	4.12		50

7	4.13		48
8	4.14		73
9	4.15		48
10	4.16		53
11	4.17		(0)
12	4.18		(4)
13	4.19		(10) (14) ^[b]
14	4.20		(12) (25) ^[b]
15	4.21		(5) (7) ^[b]
16	4.22		(14) (21) ^[b]

17	4.23		(0) (0) ^[b]
18	4.24		(0)
19	4.25		(0)

1-Chloro-4-nitrobenzene (3 mmol), piperidine (9 mmol) and *N,N'*-dimethylurea (1.5 mmol) in octane (3 mL) at 90 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra. ^[b] Carried out at 110 °C.

The reaction proved to be successful for a series of simple cyclic secondary amines. Piperidine, pyrrolidine, morpholine, 1,2,3,4-tetrahydroisoquinoline and piperazine all gave good to excellent yields (**4.2**, **4.8**, **4.9**, **4.10** and **4.11**, **Table 4.10**, entry 1-5). Functionalised piperazines were also investigated, the smaller substituted 1-methylpiperazine gave **4.14** with a yield of 73% (**Table 4.10**, entry 8), whereas the bulkier substituted 1-(2-pyrimidyl)piperazine and 1-phenylpiperazine gave more moderate yields of 50% (**4.12**) and 48% (**4.13**), respectively (**Table 4.10**, entry 6 and 7). Thiomorpholine gave **4.15** in a moderate yield of 48% (**Table 4.10**, entry 9). Interestingly 5-amino-1-pentanol gave **4.16** with a yield of 53% and a conversion of 58% (**Table 4.10**, entry 10), whereas hexylamine gave a conversion of only 12% to the corresponding secondary amine **4.20** (**Table 4.10**, entry 14). Acyclic secondary amines were not tolerated, no conversion was observed for dibenzylamine (**Table 4.10**, entry 12), and the smaller diethylamine gave only a 4% conversion to **4.18** (**Table 4.10**, entry 11), it is thought this is due to the steric demand of the functional groups. In cyclic secondary amines, the functional groups are pinned back, allowing the lone pair on the nitrogen to be more available to react, in the case of the acyclic secondary amines these functional groups have free rotation, which could lead to steric hindrance around the lone pair, making it less available to react. Apart from 5-amino-1-pentanol, primary amines were not well tolerated either, with all examples attempted giving less than 20% conversion (**Table 4.10**, entry 13-17).

Unsurprisingly when the reaction was attempted with *p*-anisidine no reaction was observed (**Table 4.10**, entry 17). As primary amines are less nucleophilic than secondary amines, due to less induction from substituents on the nitrogen, it is not surprising that the primary amines gave lower conversions, higher temperatures or catalytic loading may lead to greater conversions. As the primary amines gave such low conversions, these reactions were also attempted at an increased temperature, 110 °C. These conversions are the bracketed values under the conversions at 90 °C in **Table 4.10**, entry 13-17, although a slight increase was seen in all cases, low conversions were still observed with the highest being 25% for hexylamine. Finally indoline and 2-methylpiperidine gave no reaction (**Table 4.10**, entry 18 and 19), both the amines have a substituent at the α -position to the nitrogen, it is thought that the extra bulk near the nitrogen on the amine hinders the ability of the amine to react.

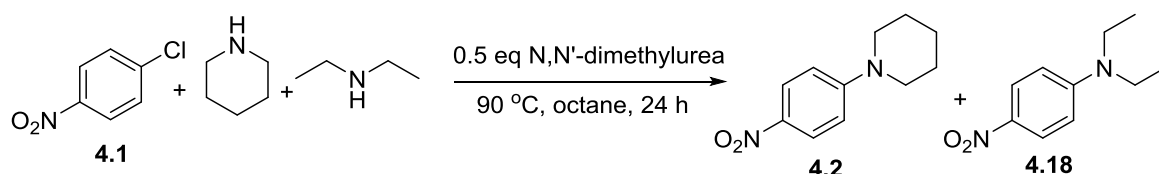


Figure 4.31: Competition experiment

Although it was assumed the reaction would be selective towards cyclic secondary amines over acyclic secondary amine, a completion experiment was run to determine if this was indeed the case. Using the same reaction conditions as the used for the substrate scope, with the addition of 3 equivalents of piperidine and 3 equivalents diethylamine, after 24 hours analysis of H^1 NMR spectra showed that the reaction had gone to completion and only product **4.2** was present, proving that the reaction was selective towards acyclic secondary amines. This could be beneficial if a substrate which contained both a cyclic and acyclic secondary amine and it was desired to preferably react at the cyclic amine.

Table 4.11: Arene substrate scope

Entry	Compound	Arene	<i>N,N'</i> -Dimethylurea Conversion (%) ^[a]	1,3-Diphenylurea Conversion (%) ^[a]	Background (%) ^[a]
1	4.26		65	59	66
2	4.27		0	0	0
3	4.28		0	0	0
4	4.29		67	62	69

Arene (1 mmol), piperidine (1.5 mmol) and *N,N'*-dimethylurea (1 mmol) in octane at 90 °C for 24 h.^[a] Conversions determined by analysis of ¹H NMR spectra.

The substrate scope of the arene was also investigated. 1-Chloro-2-nitrobenzene was investigated as it was thought this may give similar conversions to 1-chloro-4-nitrobenzene. However it was observed that although the background reaction was considerably higher, with a conversion to **4.26** of 66 % compared with 8% for 1-chloro-4-nitrobenzene. No increase in reactivity was observed on the addition of 1 equivalent of *N,N'*-dimethylurea or 1,3-Diphenylurea, with conversions of 65% and 59%, respectively. Carbonyls are also known to form hydrogen bonds with ureas to activate molecules in reactions, this possibility was also explored. To explore the activation of carbonyl groups several ketones and an aldehyde were used. Both 4-chloroacetophenone and 2'-chloroacetophenone showed no conversion in the background reaction or indeed when *N,N'*-dimethylurea or 1,3-Diphenylurea were added. 4-Chlorobenzaldehyde gave a background reaction of 69% to the corresponding amine **4.29**, however a similar conversions of 62% and 67% were observed up on the addition of 1,3-diphenylurea and *N,N'*-dimethylurea, respectively. These results suggested that the conditions developed for 1-chloro-4-nitrobenzene were not compatible with other arenes.

4.4 Conclusions

Optimised conditions were developed for the S_NAr reaction between 1-chloro-4-nitrobenzene and piperidine with *N,N'*-dimethylurea as the catalyst. The reaction was shown to give good to excellent yields with a variety of cyclic secondary amines. Unfortunately the reaction did not proceed when attempted with acyclic secondary amines, it is thought this is due to the steric hindrance as the functional groups have free rotation unlike in cyclic amines. Primary amines were not well tolerated under the optimised reaction conditions, with 5-amino-1-pentanol being the only example which gave a moderate yield.

Competition experiments demonstrated that the reaction was selective for cyclic secondary amines over acyclic secondary amines.

Attempts to explore the possible substrate scope in terms of the arene proved unsuccessful, no enhancement in conversion from the background rate was observed when the nitro group was shifted from the 4-position to the 2-position. The use of chloroarenes containing a carbonyl group instead of a nitro group all showed no increase from the background rate with the addition of a urea organocatalyst.

4.5 Future work

Though many examples of urea catalysis in the literature use more complicated, bulky ureas which have to be synthesised, the catalysts used in this investigation were simple commercially available ureas, which were relatively inexpensive. Binding studies could be conducted between urea and 1-chloro-4-nitrobenzene to determine the extent of the interaction between the two reagents. A better understanding of these interactions may enable the design of a better catalyst. The use of other ureas could be investigated, so the conditions of the reaction could be further optimised, for example: fewer equivalents of amine and a lower catalytic loading.

Although these conditions worked well for cyclic secondary amines, they did not prove as effective for other amines. The development of conditions tailored to the use of acyclic secondary amines or primary amines could be explored further.

The conditions developed in this research were only compatible with one arene, 1-chloro-4-nitrobenzene. Possible urea catalysts could be explored for greater arene compatibility, such as those that contain an aldehyde or ketone carbonyl group, to broaden the substrate scope of the arene for this type of reaction.

5 Imidazole catalysed synthesis of primary amides from unactivated carboxylic acids

5.1 Introduction

Many examples of primary amides can be found in natural products, throughout organic synthetic chemistry, as well as in areas such as pharmaceutical chemistry.¹³³

Figure 5.1 illustrates some uses of primary amides; Modafinil (**5.1**) is a psychostimulant, Temodar (**5.2**) is used as a chemotherapy drug and Keppra (**5.3**) is used as an anti-epilepsy drug. Also shown is oleamide (**5.4**), which can be used as a lubricant, but has also been shown to have a role in sleep deprivation.

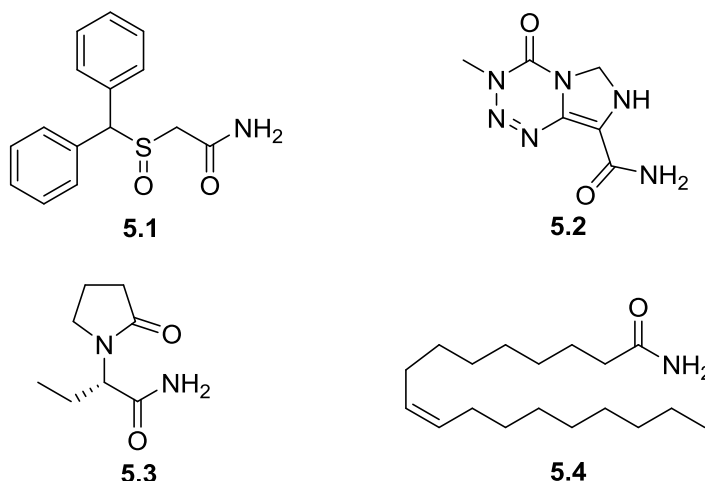


Figure 5.1: Examples of primary amides

Traditional methods of synthesising amides from carboxylic acids, require activation of the acid, followed by attack of ammonia in the case of primary amides or an amine for secondary and tertiary amides. For example, conversion of the carboxylic acid to an acid chloride followed by addition of ammonia (**Figure 5.2**). Similar activation can be carried out using common activating agents, such as DCC and HOBt.¹³⁴

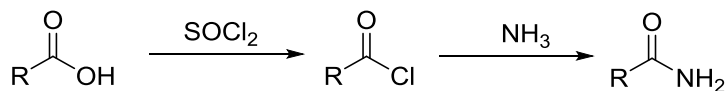


Figure 5.2: Traditional synthesis of primary amides

As ammonia is a gas, the method calls for ammoniated solvents or bubbling ammonia through the reaction solution, which can reduce atom economy. This can be overcome by using ammonium salts, Katritzky and others reported the use of ammonium hydroxide as an ammonia source, where activation of the carboxylic acid was achieved with *N*-(1-methanesulfonyl)benzotriazole a HOBt derivative

(**Figure 5.3**), quantitative yields were achieved with various acids. The activated *N*-acylbenzotriazole proceeded to the amide in 2-4 hours at room temperature.¹³⁵

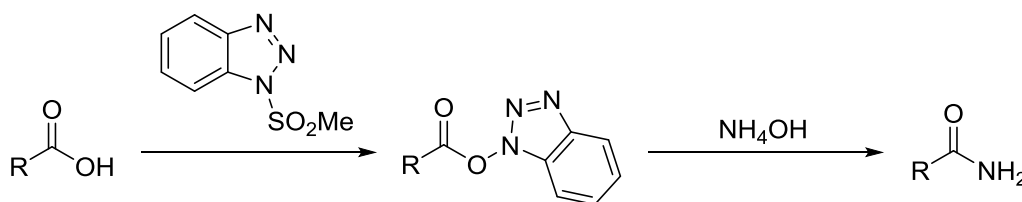


Figure 5.3: Activation of carboxylic acid with 1-(trimethylsilyl)benzotriazole

Bailén *et al.* reported 2-mercaptopyridone-1-oxide uronium salts (**Figure 5.4**) as a cheaper alternative to HOBt derivatives in the preparation of primary amides, NH_4Cl is used as the ammonia source. Good to excellent yields of 46% to 99% were obtained for a range of carboxylic acids.¹³⁶

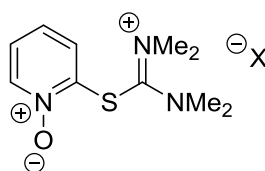


Figure 5.4: 2-Mercaptopyridone-1-oxide uronium salts

The direct synthesis of primary amides from carboxylic acids through activation by imidazole was reported by Khalafi-Nezhad and others. The reactions were carried out with urea as the nitrogen source and a stoichiometric amount of imidazole using a conventional 300 W microwave oven, for 90-360 seconds. Yields of 47 to 85% were gained for various aromatic acids.¹³⁷

Although the methods above all demonstrate the preparation of primary amides in very good yields, the need for the addition of an activating agent in stoichiometric amounts, results in poor atom efficiency in all cases. Therefore the preparation of primary amides through catalytic methods has been an area of interest, for several decades.

Shteinberg report the synthesis of 4-nitrobenzamide from 4-nitrobenzoic acid catalysed by boric acid or tetrabutoxytitanium, the reaction was aided by the addition of a cocatalyst, PEG-400 (polyethylene glycol) (**Figure 5.5**). A series of catalysts was investigated, with no conversion observed, it was found the addition of a catalytic amount of PEG-400 was also needed as a cocatalyst, boric acid and tetrabutoxytitanium were found to give the best results with yields of 92% and 90%,

respectively.¹³⁸ This work was furthered by exploration of the solvent, it was found aprotic solvents at 145 – 177 °C gave the optimum results.¹³⁹ The size of the PEG molecule was also investigated, it was determined that short polyethylene groups and crown ether gave no reaction. It was found after six hours PEG-115 outperformed other sizes with 73 % yield, but after 12 hours PEG-13, -115, -400, 1000 and -2000 all gave near quantitative yields.¹⁴⁰

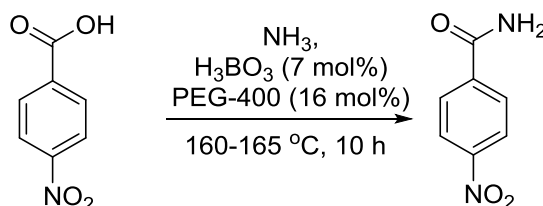


Figure 5.5: Synthesis of 4-nitrobenzamide

Reddy *et al.* reported the synthesis of primary amides from carboxylic acids promoted by zirconyl chloride under microwave irradiation, with urea as a nitrogen source (**Figure 5.6**). A series of benzoic and phenylacetic acids with electron withdrawing and donating groups were tolerated well. The reactions were run in the solid phase and it was demonstrated that the catalyst could be recycled twice with no significant decrease in yield.¹⁴¹

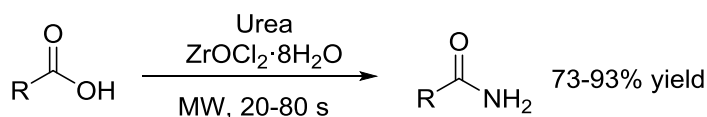


Figure 5.6: Zirconyl chloride catalysed amide synthesis

The same group reported the use of urea in the conversion of carboxylic acids to primary amides catalysed by ceric ammonium nitrite a year later. Again the reaction was carried out in the solid state under microwave irradiation. Very good to excellent yields were gained for a range of aromatic acids (77-92%), with time varying from one to three minutes.¹⁴²

Tinnis and others reported the catalysed synthesis of primary amides from carboxylic acids, with ammonium carbamates as the ammonium source (**Figure 5.7**). In a catalyst screen with phenylacetic acid, TiCl₄ gave quantitative yields of phenylacetamide, with ZrCl₄ also showing promise with a yield of 75%. Substrate scope was explored using both catalysts, although in the majority of cases TiCl₄ gave

the best conversions, ZrCl_4 did outperform it in some instances. Good to excellent of yields of 42 to 99% were gained for a range of functionalities. It was also shown that *N,N*-dimethylamides could be synthesised under the same conditions with dimethylammonium dimethylcarbamate as the nitrogen source.¹⁴³

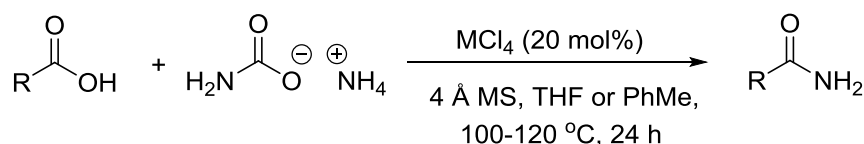


Figure 5.7: Direct amidation of carboxylic acids

As well as synthesis of primary amides from carboxylic acid, other starting functional groups can also undergo transformation to primary amides. Schnyder *et al.* reported using formamide as the nitrogen source in the aminocarboxylation of aryl halides to produce primary amides (**Figure 5.8**). Quantitative conversions and moderate to good yields of 34% to 82% were obtained for various aryl and pyridyl bromides. It was also demonstrated that secondary and tertiary amides could be synthesised in very good yields when the formamide is substituted with *N*-methylformamide and dimethylformamide, respectively.¹⁴⁴

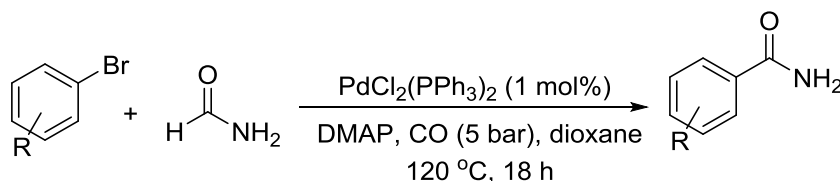


Figure 5.8: Aminocarboxylation of aryl halides

The rhodium catalysed synthesis of primary amides from aldoximes and aldehydes was reported by Fujiwara and others (**Figure 5.9**). A range of linear and branched aldoximes as well as aromatic oximes gave quantitative conversions in most cases and excellent yields. Quantitative conversions were also gained for the aldehyde analogues of some of those examples. The proposed mechanism suggests that water is not only the solvent, but also plays a role in the reaction.¹⁴⁵

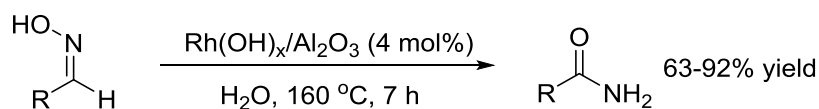


Figure 5.9: Primary amides from aldoximes

Allen and others reported the rearrangement of oximes to yield primary amides using simple indium and zinc salts. A series of aliphatic and aromatic oximes was investigated using both catalyst system (**Figure 5.10**). Although the zinc system outperformed the indium in some instances, there are many examples where comparable yields were obtained for both, even with the indium system having a much lower catalyst loading.¹⁴⁶

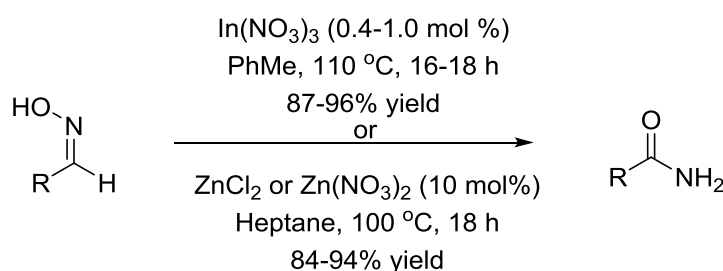


Figure 5.10: Oxime to primary amide

The synthesis of primary amides from iodides *via* aminocarbonylation followed by deprotection was reported by Takács *et al.* in 2007. The two step reaction involves the formation of an *N-tert*-butyl amide, this is followed by selective cleavage of the *tert*-butyl group to give the primary amide (**Figure 5.11**). Yields of 52% to 98% were obtained for various iodo alkenes and aromatics. The system was also demonstrated for the synthesis of ketoamides.¹⁴⁷

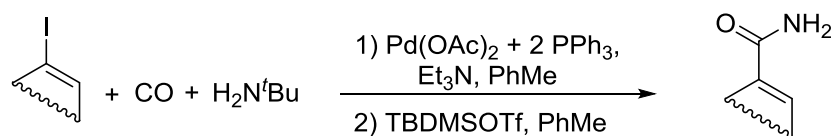


Figure 5.11: Aminocarbonylation of iodides

Veitch and others demonstrated the synthesis of primary amides from esters, with magnesium nitride as the nitrogen source (**Figure 5.12**). Optimised conditions gave good to excellent yields for a range of aromatic, aliphatic and cyclic substituents in the R¹ position. It was demonstrated that the R² position could tolerate methyl, ethyl, *iso*-propyl and *tert*-butyl groups, with little effect on the yields. Although the reaction was originally attempted under microwave irradiation, it is thought that decomposition of the starting material took place, so conventional heating was used.¹⁴⁸

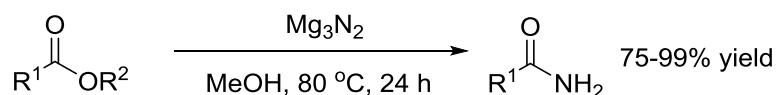


Figure 5.12: Primary amides from esters

The synthesis of primary amides from ketones and alcohols was reported by Cao *et al.* (Figure 5.13). The system employed aqueous ammonia and iodine to achieve a direct transformation. The reaction was shown to work with a series of electron rich and poor aromatic ketones with yields of 57% to 96%. The proposed mechanism suggested the reaction proceeds through the displacement of the hydrogens on the terminal methyl group with iodides, before attack of the carbonyl by ammonia. Good yield were also obtained for the transformation of several 1-arylethanols to primary amides under the same conditions.¹⁴⁹

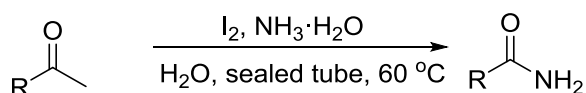


Figure 5.13: Direct amide formation from ketones

Ali and Punniyamurthy reported the palladium catalysed one-pot conversion of aldehydes to primary amides, with hydroxylamine hydrochloride as the nitrogen source (Figure 5.14). The reaction was demonstrated to tolerate electron rich and poor aromatics, with substituents in the *ortho*, *meta*, and *para* positions, as well as aliphatic aldehydes in good to excellent yields (65-98%).¹⁵⁰

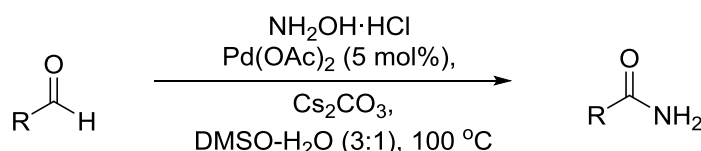
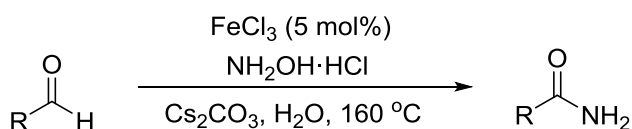


Figure 5.14: One-pot synthesis of amides from aldehydes

The iron catalysed synthesis of primary amides from aldehydes was reported by Gowda and Chakraborty (Figure 5.15). The reaction is carried out in water with hydroxylamine hydrochloride as the nitrogen source. The FeCl_3 catalysed reaction was shown to tolerate aryl, alkyl and allyl aldehydes, including branched and bulky examples with excellent yields of 85% to 96%.¹⁵¹

Figure 5.15: FeCl_3 catalysed amide synthesis

Yamaguchi and co-workers reported the conversion of primary alcohols to primary amides under an atmosphere of oxygen catalysed by manganese oxide on octahedral molecular sieves (OMS), as a heterogeneous catalyst (**Figure 5.16**). As well as gaining excellent yields for a series of aromatic primary alcohols (65-99%), it was shown that similar reaction conditions could be used to convert aldehydes and nitriles to primary amides. The only difference being that the nitrile reactions were carried out under an atmosphere of argon instead of oxygen.¹⁵²

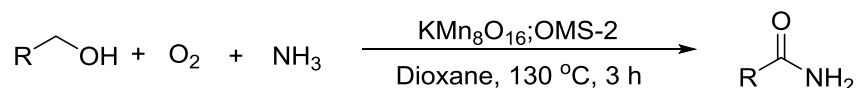


Figure 5.16: Conversion of primary alcohol to primary amide

The selective hydration of nitriles was reported by Chen and others (**Figure 5.17**). The superbase system CsOH-DMSO generates a dimethylsulfinyl anion *in situ* which catalyses the hydration. After optimisation, the reaction was shown to give very good yields for electron rich and poor aromatic aldehydes, along with a series of pyridine derivatives and aliphatic systems.¹⁵³

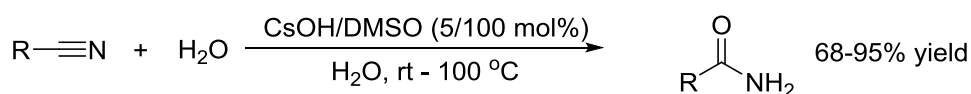


Figure 5.17: Hydration of nitriles

Song *et al.* reported the synthesis of primary amides from aerobic decarboxylation ammoxidation of phenylacetic acid derivatives, catalysed by copper (**Figure 5.18**). Electron donating and withdrawing groups were tolerated in the *ortho*, *meta*, and *para* positions of the phenylacetic acid in moderate to good yields (32-90%). It was also demonstrated that the same conditions could be used to synthesise primary amides from α -hydroxyphenylacetic acid in moderate to good yields.¹³³

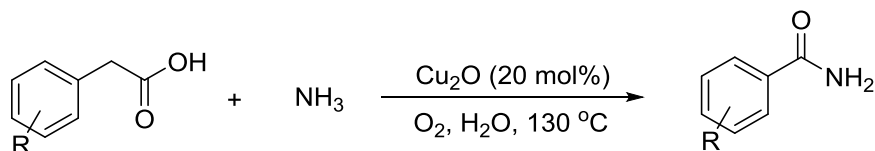


Figure 5.18: Aerobic decarboxylation ammoxidation of phenylacetic acid

Although there are many excellent examples of primary amide syntheses from various starting materials, there is still room for exploration especially in the area of organocatalysed reactions.

5.2 Aims and objectives

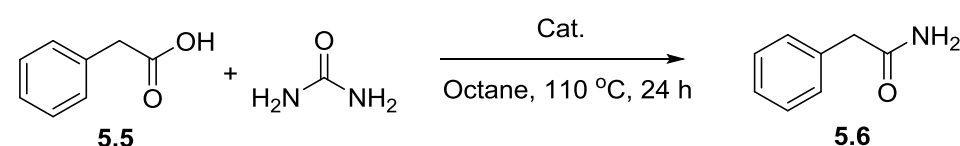
Due to the applicability of primary amides we intended to develop a cheap and versatile method of synthesising primary amides from unactivated carboxylic acids. To achieve this we aimed to find a readily available and inexpensive organocatalyst and nitrogen source and to carry the reaction out under relatively mild conditions.

5.3 Results and discussion

5.3.1 Catalyst screen

An initial catalyst screen carried out by Dr Rosie Chhatwal showed that DMAP (4-Dimethylaminopyridine) and imidazole both showed promise as potential organocatalysts in the formation of primary amides from carboxylic acids, using urea as a nitrogen source. These experiments were initially repeated to confirm the activity of the organocatalysts.¹⁵⁴

Table 5.1: Catalyst screen with 1.0 equivalent of urea



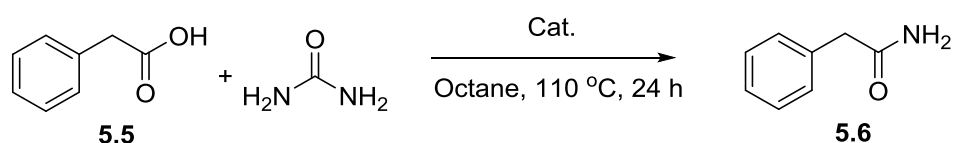
Entry	Catalyst	Catalyst (Equiv)	Conversion ^[a] (%)
1	Background	0	24
2	Imidazole	0.1	59
3	Imidazole	0.2	78
4	DMAP	0.1	58
5	DMAP	0.2	71

Phenylacetic acid (1 mmol), urea (1 mmol) and catalyst in octane (1 mL) at 110 °C for 24 h.

^[a] Conversions determined by analysis of ¹H NMR spectra.

These initial experiments used one equivalent of both phenylacetic acid (**5.5**) and urea at 110 °C for 24 hours, both imidazole and DMAP improved the conversion of **5.5** into **5.6** compared with the background reaction conversion of 24% (**Table 5.1**, entry 1). With a catalytic loading of 0.1 equivalents, imidazole and DMAP gave comparable conversions of 59% and 58%, respectively (**Table 5.1**, entries 2 and 4). At a higher catalytic loading of 0.2 equivalents, imidazole gave a slightly higher conversion to **5.6** of 78% compared with that of DMAP of 71% (**Table 5.1**, entries 3 and 5). As there wasn't a large difference in conversions between imidazole and DMAP at this point it was decided to continue the optimisation using both organocatalysts.

Table 5.2: Catalyst screen with 1.5 and 2.0 equivalents of urea



Entry	Catalyst	Catalyst (Equiv)	1.5 equiv urea Conversion ^[a] (%)	2.0 equiv urea Conversion ^[a] (%)
1	Background	0	24	25
2	Imidazole	0.1	71	72
3	Imidazole	0.2	86	84
4	Imidazole	0.3	85	-
5	DMAP	0.1	74	71
6	DMAP	0.2	84	84

Phenylacetic acid (1 mmol), urea and catalyst in octane (1 mL) at 110 °C for 24 h. ^[a] Conversions determined by analysis by analysis of ¹H NMR spectra

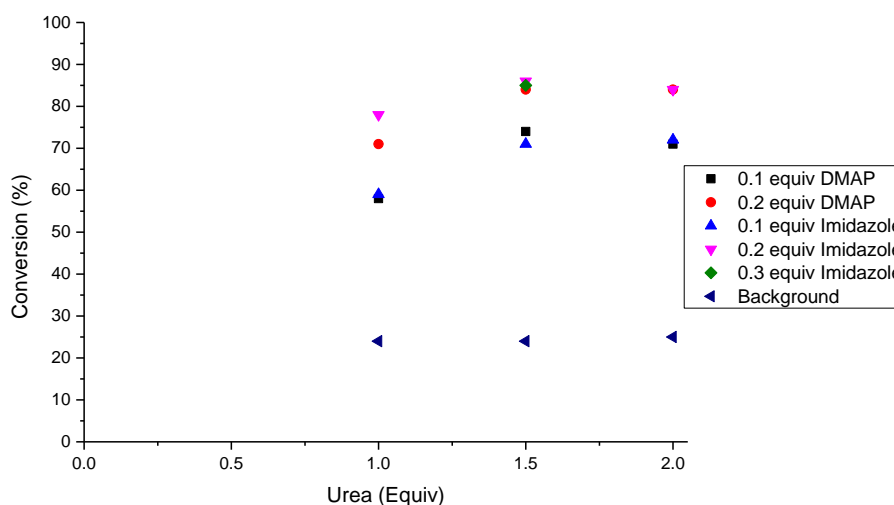


Figure 5.19: Exploration of catalyst loading and urea concentration

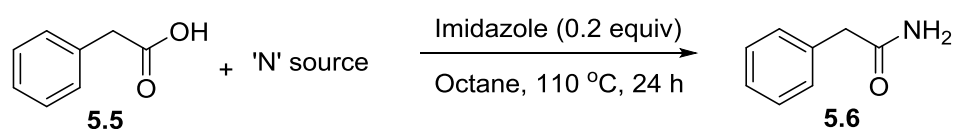
The amount of urea was increased to 1.5 equivalents with respect to the acid (**5.5**) and the catalyst loading was further explored. For the case of imidazole, there was an increase in conversion between 0.1 and 0.2 equivalents of catalyst, 71% to 86% (**Table 5.2**, entries 2 and 3), but when the catalyst loading was increased to 0.3 equivalents, no further improvement in conversion was observed (**Table 5.2**, entry 4). Again DMAP gave similar conversions to imidazole, with conversions of 74% and

84% for catalytic loading of 0.1 and 0.2 equivalents, respectively (**Table 5.2**, entries 5 and 6). An increase in the number of equivalents of urea to two had little effect on the conversion compared with 1.5 equivalents in either case, for 0.1 equivalents of imidazole a comparable conversion of 71 and 72% was observed (**Table 5.2**, entry 2), but a decrease from 86% to 84% was observed for a catalyst loading of 0.2 equivalents of imidazole (**Table 5.2**, entry 3). Similarly, a small decrease in conversion from 74% to 71% was observed for 0.1 equivalents of DMAP (**Table 5.2**, entry 5) and the conversion for 0.2 equivalents of DMAP, did not alter, remaining at 84% (**Table 5.2**, entry 6). **Figure 5.19** allows for easy comparison of these results. These results suggest that the addition of 1.5 equivalents of urea and a catalytic loading of 0.2 equivalents, with respect to the carboxylic acid, are the optimum conditions.

5.3.2 Nitrogen source

A similar reaction has recently been developed in our group, catalysed by $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ with urea as the nitrogen source,¹⁵⁴ this led to using urea as a starting point in this work as well. To ensure this was the best nitrogen source for our organocatalysts, a series of other possible sources was screened, including a range of ammonium salts.

Table 5.3: 'N' Source screen



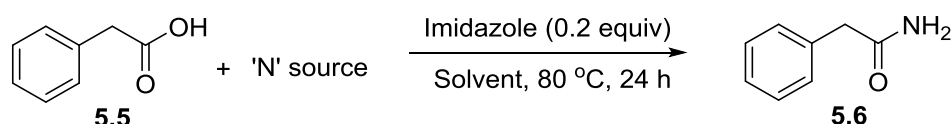
Entry	'N' source	Conversion (%) ^[a]
1	Urea	86
2	Ammonium chloride	0
3	Ammonium formate	19
4	Ammonium acetate	20
5	Ammonium iodide	0
6	Ammonium carbamate	13
7	Formamide	32

Phenylacetic acid (1 mmol), N source (1.5 mmol) and imidazole (0.2 mmol) in octane (1 mL) at 110 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra

Of the ammonium salts tested, ammonium chloride and ammonium iodide gave no conversion (**Table 5.3**, entries 2 and 5). While some conversion was observed with ammonium formate, ammonium acetate and ammonium carbamate, 19%, 20% and 13%, respectively (**Table 5.3**, entries 3, 4 and 6). Formamide was shown to demonstrate a slightly improved conversion of 32% (**Table 5.3**, entry 7). Though urea outperformed all other nitrogen sources considerably, with a conversion of 86% (**Table 5.3**, entry 1).

5.3.3 Solvent screen

Table 5.4: Solvent screen



Entry	Solvent	Urea Conversion (%) ^[a]	Formamide Conversion (%) ^[a]
1	Water	0	0
2	1-Propanol	0	0
3	Ethanol	0	0
4	Ethyl acetate	0	0
5	Octane	10	6
6	Cyclohexane	8	8
7	Toluene	5	8
8	2-MethylTHF	0	0

Phenylacetic acid (1 mmol), N source (1.5 mmol) and imidazole (0.2 mmol) in octane (1 mL) at 80 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra

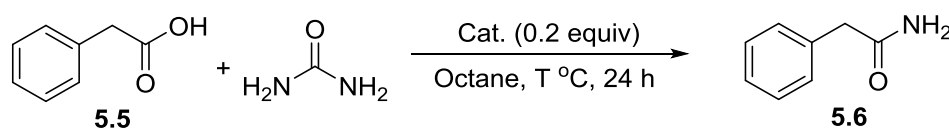
A solvent screen was performed to determine if there was a more suitable solvent for the reaction than octane. Solvents were chosen in an attempt to maintain the sustainability of the reaction, as such some of the solvents selected had lower boiling points, therefore the screen was run at 80 °C. The reaction did not proceed in water, alcohols, ethyl acetate or 2-methylTHF (**Table 5.4**, entries 1, 2, 3, 4 and 8). Some conversion was observed in cyclohexane and toluene as well as octane, and

though the conversions are all close to each other, some information can be taken from them. The highest conversion was observed in octane with urea as the nitrogen source at 10%, with a lower conversion observed with formamide at 6% (**Table 5.4**, entry 5). Although comparable conversions of 8% were observed for both urea and formamide in cyclohexane (**Table 5.4**, entry 6), as the boiling point of cyclohexane is 80 °C, there is little scope for exploring the temperature further. A higher conversion was observed of 8% for formamide in toluene, with only 5% being achieved when urea was used (**Table 5.4**, entry 7).

5.3.4 Temperature screen

It was decided that octane would be used as the reaction solvent, as the highest conversion was obtained in octane. Also the boiling point of octane is 126 °C compared with 110 °C for toluene, meaning there is a greater scope when exploring the temperature of the reaction.

Table 5.5: Temperature screen



Entry	Temperature (°C)	Imidazole Conversion (%) ^[a]	DMAP Conversion (%) ^[a]	Background Conversion (%) ^[a]
1	80	10	8	3
2	90	27	24	7
3	100	50	48	15
4	110	86	84	24
5	120	96	90	33
6	126	96	89	37

Phenylacetic acid (1 mmol), urea (1.5 mmol) and imidazole (0.2 mmol) or DMAP (0.2 mmol) in octane (1 mL) at T °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra

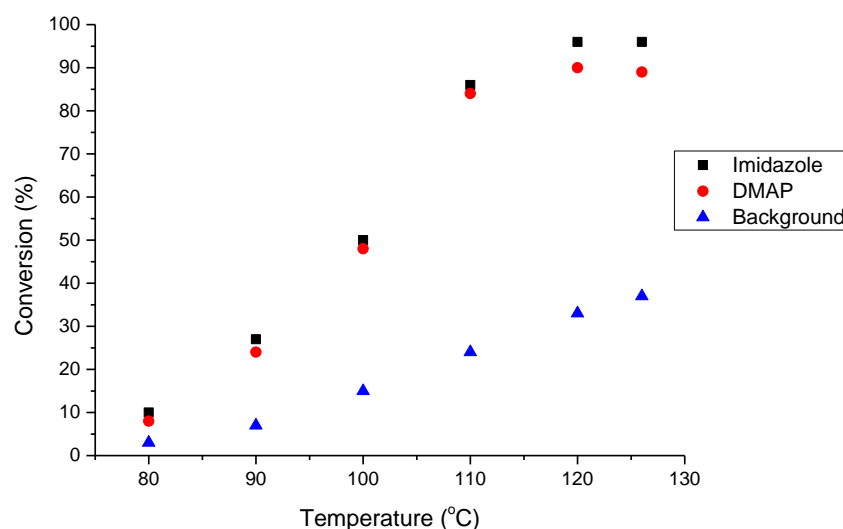


Figure 5.20: Temperature screen

The reaction was run at 80, 90, 100, 110, 120 and 126 °C using both imidazole and DMAP as the catalyst to determine the optimum temperature of the reaction (**Figure 2.20**). Between 80 and 110 °C there was very little difference in conversion between DMAP and imidazole (**Table 5.5**, entries 1, 2, 3 and 4). At 120 °C, it was seen that imidazole outperformed DMAP, with a conversion of 96% compared with 90% for DMAP (**Table 5.5**, entry 5). Increasing the temperature further to the boiling point of octane, 126 °C, gave no improvement in conversion (**Table 5.5**, entry 6).

5.3.5 Concentration study

Finally, the concentration of the reaction was investigated, all optimisation reactions had been carried out at 1 M with respect to the phenylacetic acid. A more concentrated and a less concentrated reaction were carried out to determine if the reaction could be further improved.

Table 5.6: Concentration study

Entry	Molarity (M)	Imidazole Conversion (%) ^[a]	DMAP Conversion (%) ^[a]	Background Conversion (%) ^[a]
1	0.5	87	88	28
2	1.0	98	91	33
3	2.0	95	90	34

Phenylacetic acid (1 mmol), urea (1.5 mmol) and imidazole (0.2 mmol) or DMAP (0.2 mmol) in octane (1 mL) at T °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra

When the concentration of the reaction was reduced to 0.5 M, a decrease in conversion was observed compared with the 1 M reactions, an 11% decrease was observed for the imidazole reaction, with a small decrease of 3% in the DMAP case (**Table 5.6**, entry 1). Comparable conversions were obtained when the concentration was increased, with a slight decrease of 3% when imidazole was the catalyst and only 1% decrease in the DMAP reaction (**Table 5.6**, entry 3). Suggesting increasing the concentration above 1 M has no effect on the reaction.

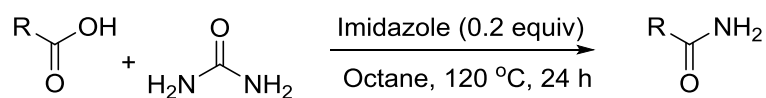
5.3.6 Price considerations

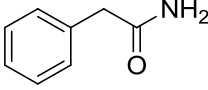
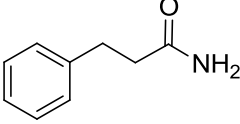
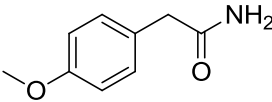
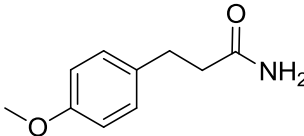
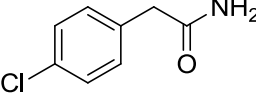
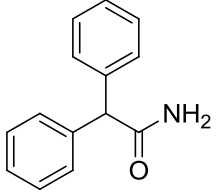
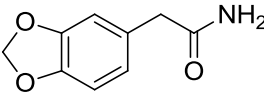
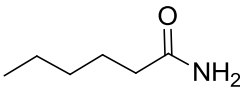
Although imidazole and DMAP gave similar results throughout the optimisation process, imidazole consistently outperformed DMAP. To determine if there was much difference in cost of the imidazole and DMAP, price comparisons were carried out. Imidazole costs £40.00 for 500 g and DMAP costs £325.90 for 500g (prices taken from Fisher Scientific, <http://www.fisher.co.uk/>, on the 11/08/2015), this equates to £5.45 and £79.68 per mole, respectively, meaning DMAP is 14.6 times more expensive than imidazole. Taking into account the higher conversion and lower cost, imidazole was chosen as the catalyst.

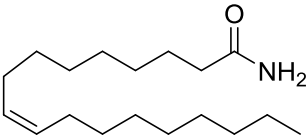
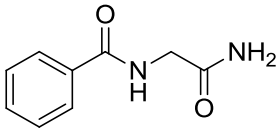
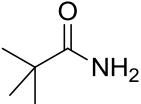
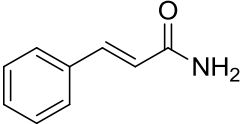
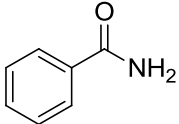
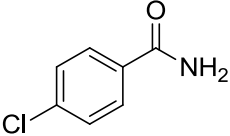
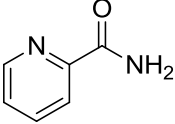
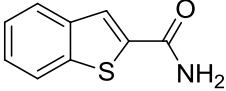
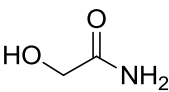
Optimised conditions were therefore one equivalent of carboxylic acid, 1.5 equivalents of urea and 0.2 equivalents of imidazole in octane at 120 °C for 24 hours. The pure product could be obtained through dissolving the reaction mixture in ethyl acetate and washing with saturated sodium bicarbonate solution three times, followed by extraction of the aqueous layer 5 times with ethyl acetate.

5.3.7 Substrate Scope

Table 5.7: Acid substrate scope with urea



Entry	Compound	Product	Yield (%) (Conversion (%)) ^[a]
1	5.6		91
2	5.7		97
3	5.8		81
4	5.9		90
5	5.10		96
6	5.11		68
7	5.12		90
8	5.13		89

9	5.14		91
10	5.15		(28)
11	5.16		(26)
12	5.17		(38)
13	5.18		(30)
14	5.19		(18)
15	5.20		(65)
16	5.21		(31)
17	5.22		(67)

Carboxylic acid (3 mmol), urea (4.50 mmol) and imidazole (0.6 mmol) in octane at 120 °C for 24 h.^[a]
 Conversions determined by analysis of ¹H NMR spectra.

The substrate scope of the carboxylic acid was investigated using the optimised conditions and the reaction was seen to be applicable to a wide variety of acids. Phenylacetic acid and hydrocinnamic acid proceed to their corresponding amides **5.6** and **5.7** in excellent yields of 91% and 97%, respectively (**Table 5.7**, entries 1 and 2). In both cases functionalising the ring in the 4 position with an electron donating methyl ether, had little effect on the conversion, 4-methoxyphenylacetic acid and 3-

(4-methoxyphenyl)propionic acid gave very good yields of 81% (**5.8**) and 90% (**5.9**) (**Table 5.7**, entries 3 and 4), whilst the electron withdrawing 4-chlorophenylacetic acid gave complete conversion with a 96% yield of the corresponding amide **5.10** (**Table 5.7**, entry 5). Aliphatic groups were also tolerated, hexanoic acid gave an 89 % yield of hexanamide **5.13** (**Table 5.7**, entry 8). The bulkier diphenylacetic acid demonstrated a slightly lower yield of 68% (**5.11**, **Table 5.7**, entry 6) and 3,4-(methylenedioxy)phenylacetic acid offered a yield of 90% (**5.12**, **Table 5.7**, entry 7). Oleic acid gave an excellent yield of the corresponding oleamide (**5.14**) of 91%. Hippuric acid did not perform as well, with only 28 % conversion to **5.15** (**Table 5.7**, entry 9) similarly the more branched pivalic acid only proceeded to 26% conversion to **5.16** (**Table 5.7**, entry 10). The unsaturated version of hydrocinnamic acid, *trans*-cinnamic acid only offered a conversion to **5.17** of 38% (**Table 5.7**, entry 11). Unsurprisingly, benzoic acids did not perform particularly well, benzoic acid proceeded to **5.18** in 30% conversion (**Table 5.7**, entry 13) and 4-chlorobenzoic acid to **5.19** with only 18% conversion (**Table 5.7**, entry 14). This lower conversion is consistent with the electron withdrawing character of the chlorine on the ring. 2-Picolinic acid performed better than its benzylic counterparts with a conversion into **5.20** of 65% observed (**Table 5.7**, entry 15), however problems were encountered during purification, as much of the product was lost in the aqueous layer and the product which was obtained was not pure. Glycolic acid presented the same problem (**Table 5.7**, entry 17), although a conversion to corresponding amide **5.22** of 67% was obtained, problems were encountered during purification. The sulfur containing carboxylic acid only proceeded to **5.21** in 31% conversion (**Table 5.7**, entry 16).

The possibility of using functionalised ureas to synthesise secondary amides was also explored. Using the original conditions in a trial reaction between phenylacetic acid and *N,N'*-dimethylurea afforded a conversion of 54% to the secondary amide **5.23**. Whilst increasing the temperature showed an improvement in conversion, a further increase in the equivalents of the urea to two equivalents was needed to obtain adequate conversions.

Table 5.8: Substrate scope with *N,N'*-dimethylurea

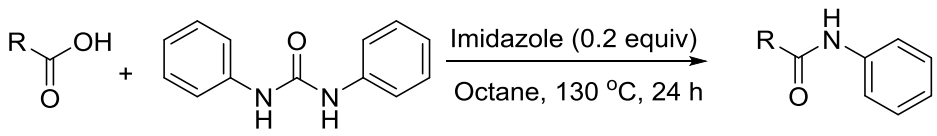
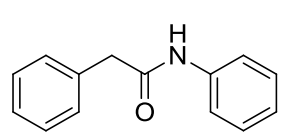
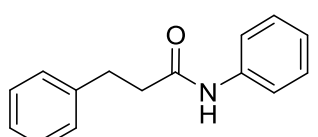
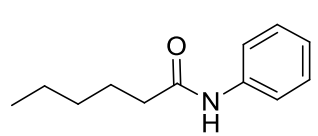
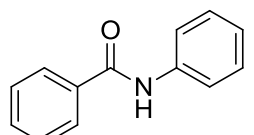
$ \begin{array}{c} \text{R}-\text{C}(=\text{O})\text{OH} + \text{H}-\text{N}(\text{CH}_3)-\text{C}(=\text{O})-\text{N}(\text{CH}_3)-\text{H} \\ \xrightarrow[\text{Octane, 130 } ^\circ\text{C, 24 h}]{\text{Imidazole (0.2 equiv)}} \\ \text{R}-\text{C}(=\text{O})\text{N}(\text{CH}_3)-\text{H} \end{array} $			
Entry	Compound	Product	Yield (%) (Conversion (%)) ^[a]
1	5.23		69
2	5.24		67
3	5.25		80
4	5.26		72
5	5.27		52
6	5.28		(29)
7	5.29		(25)
8	5.30		(45)

Carboxylic acid (3 mmol), *N,N'*-dimethylurea (6.00 mmol) and imidazole (0.6 mmol) in octane at 130 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

Using these conditions *N,N'*-dimethylurea was used to synthesise a range of *N*-methyl amides. Both phenylacetic acid and hydrocinnamic acid were tolerated well and gave **5.23** and **5.24** in good yields, 69 and 67%, respectively (**Table 5.8**, entries 1

and 2). Good yields of amides **5.25** and **5.26** were obtained from 4-methoxyphenylacetic acid and 3-(4-methoxyphenyl)propionic of 80% and 72%, respectively (**Table 5.8**, entries 3 and 4). A decrease in yield was observed for hexanoic acid compared with the urea example, with a yield of 52% of the corresponding secondary amide **5.27** (**Table 5.8**, entry 5). Only 29% conversion to amide **5.28** was observed for the bulky diphenylacetic acid (**Table 5.8**, entry 6) and benzoic acid only proceed to 25% conversion to the corresponding amide **5.29** (**Table 5.8**, entry 7). 2-Picolinic acid again outperformed benzoic acid **5.30**, with a conversion of 45% (**Table 5.8**, entry 8).

Table 5.9: Substrate scope with 1,3-diphenylurea

			
Entry	Compound	Product	Conversion (%) ^[a]
1	5.31		42
2	5.32		33
3	5.33		33
4	5.34		9

Carboxylic acid (3 mmol), 1,3-diphenylurea (6.00 mmol) and imidazole (0.6 mmol) in octane at 130 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

The bulkier 1,3-diphenylurea was also used to synthesise *N*-phenylamides, although lower conversions were seen in this instance. Phenylacetic acid proceeded to 42% of the corresponding amide **5.31** (**Table 5.9**, entry 1), with hydrocinnamic acid only proceeding to 33% of *N*,3-diphenylpropanamide (**5.32**, **Table 5.9**, entry 2). Similarly, hexanoic acid gave **5.33** with a conversion of 33% (**Table 5.9**, entry 3) and benzoic acid only proceeded to **5.34** in 9% conversion (**Table 5.9**, entry 4).

5.3.7.1 Other ureas

The reaction was also attempted with a tetra substituted urea, tetramethylurea, with the hope of forming a tertiary amide (**Figure 5.21**).

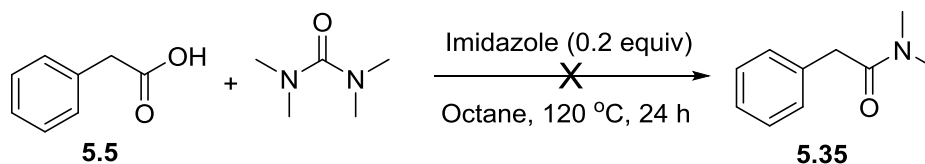
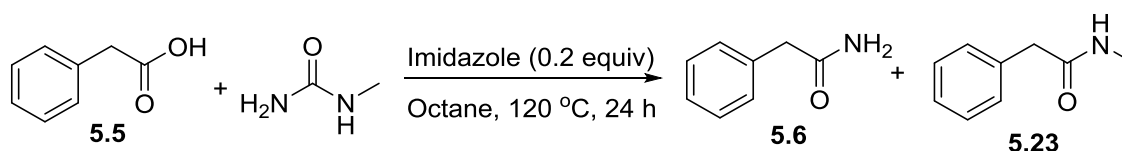


Figure 5.21: Reaction with tetramethylurea

Using the optimised reaction conditions, with two equivalents of the urea, at 120 °C for 24 hours, no conversion into the product **5.35** was observed.

To investigate the selectivity of the reaction of substituted urea compared with unsubstituted ureas, asymmetrical ureas were used as the nitrogen source.

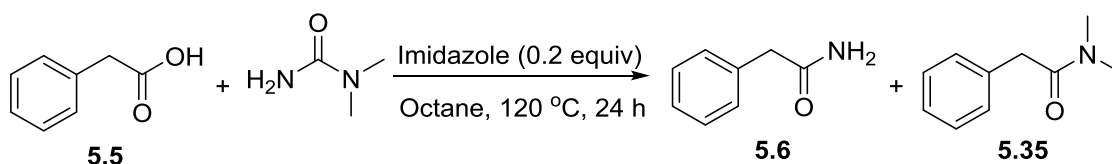
Table 5.10: Reaction with *N*-methylurea



Entry	Catalyst	Product 5.6 Conversion (%) ^[a]	Product 5.23 Conversion (%) ^[a]
1	Yes	10	77
2	No	5	40

Phenylacetic acid (1 mmol), methylurea (2 mmol) and imidazole (0.2 mmol) in octane (1 mL) at 120 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

With methylurea as the asymmetric urea, in both the case with (**Table 5.10**, entry 1) and without (**Table 5.10**, entry 2) the catalyst, the formation of the secondary amide **5.23** was favoured over the formation of the primary amide **5.6**. This can be explained by the greater nucleophilicity of the substituted nitrogen on the urea, due to the donation of electron density from the methyl group. In both cases the ratio of primary to secondary amide is the same (11:88). It can be noted that the conversion with the catalyst present is comparable with that of the reaction with *N,N'*-dimethylurea (72%).

Table 5.11: Reaction with *N,N*-dimethylurea

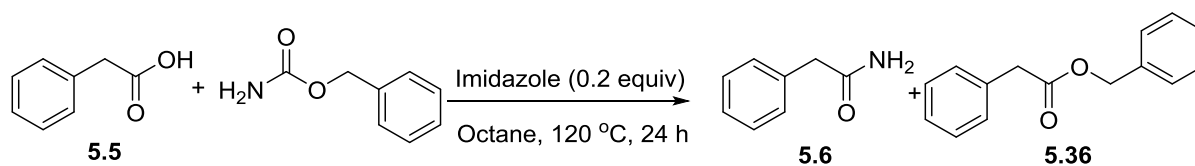
Entry	Catalyst	Product 5.6 Conversion (%) ^[a]	Product 5.35 Conversion (%) ^[a]
1	Yes	14	75
2	No	3	36

Phenylacetic acid (1 mmol), *N,N*-dimethylurea (2 mmol) and imidazole (0.2 mmol) in octane (1 mL) at 120 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

With the lack of activity observed when tetramethylurea was used, it was expected that *N,N*-dimethylurea would favour the formation of the corresponding primary amide. Surprisingly, not only did we observe the formation of the tertiary amide **5.35**, but it was also the major product. When the catalyst was present the observed conversion to the tertiary amide **5.35** was 75% with only 14% conversion to the primary amide **5.6** (Table 5.11, entry 1). Similarly without the catalyst 36% conversion to the tertiary amide **5.35** and only 3% to the primary **5.6** was observed (Table 5.11, entry 2). Again this can be explained the greater nucleophilicity of the doubly substituted nitrogen compared with the unsubstituted nitrogen on the urea, making the dimethyl nitrogen more reactive and therefore leading to the observed major product.

The possibility of using carbamates as the nitrogen source was also examined.

Table 5.12: Reaction with benzylcarbamate



Entry	Catalyst	Product 5.6 Conversion (%) ^[a]	Product 5.36 Conversion (%) ^[a]
1	Yes	17	14
2	No	10	2

Phenylacetic acid (1 mmol), benzylcarbamate (2 mmol) and imidazole (0.2 mmol) in octane (1 mL) at 120 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

Formation of both the amide product **5.6** and ester product **5.36** was observed, with the amide as the major product. Although there was a large decrease in

conversion compared with when urea is used with only 17% conversion to the amide **5.6** and 14% to the ester **5.36**, with the catalyst present (**Table 5.12**, entry 1), suggesting the carbamate is less reactive.

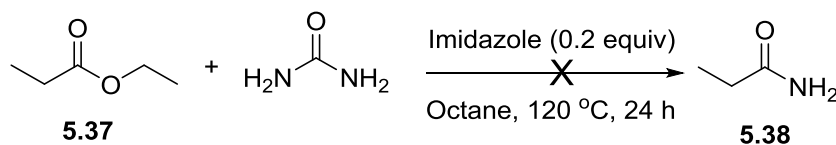


Figure 5.22: Ester as acyl donor

As discussed in the introduction amides can also be prepared from acyl groups other than acids, although the use of esters is not widely reported. Therefore the use of esters as acyl donors was investigated as an interesting alternative to carboxylic acids (**Figure 5.22**). Under optimised conditions ethyl propanoate (**5.37**) gave no conversion into the desired amide **5.38** according to analysis of crude ^1H NMR spectra.

5.3.8 Mechanistic studies

To try and propose a viable mechanism for the reaction, an investigation was carried out into the possible routes that the reaction could proceed through. It was thought that the reaction could go *via* two possible routes; decomposition of the urea followed by addition of ammonia (**Figure 5.23**, equation 1) or formation of an *N*-acylurea intermediate (**Figure 5.23**, equation 2).

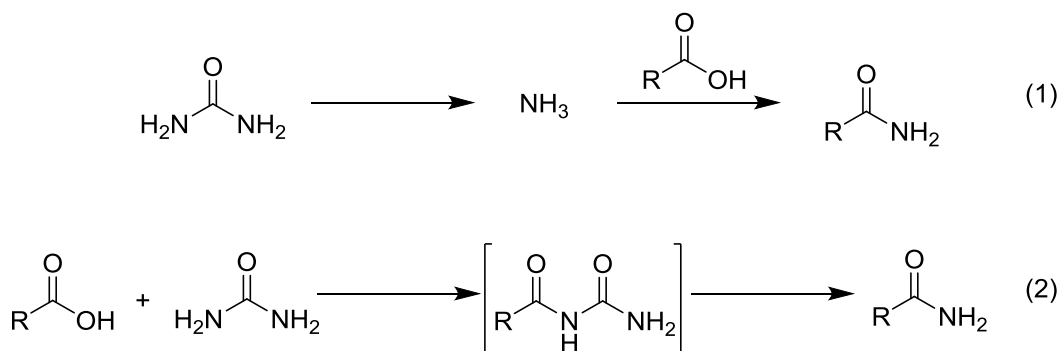


Figure 5.23: Possible reaction routes

5.3.8.1 Decomposition of urea

The decomposition of urea is known to take place at temperatures above 152 °C as reported by Schaber *et. al.*¹⁵⁵ but as in our optimised conditions the reactions were only heated to 120 °C the possibility of catalytic degradation was investigated. To investigate this possibility (**Figure 5.23**, equation 1), urea and imidazole were mixed

under optimised reaction conditions for 24 hours. Once the solvent had been removed, the weight of the reaction mixture was taken, the initial weight of the reagents was 103.7 mg, the weight after being exposed to the reaction condition was 100 mg, 96 % of material was recovered. This would suggest that degradations had not taken place, as NH_3 and CO_2 are the degradation products and as they are both gases a decrease in weight would be expected. Interpretation of the NMR of the reaction mixture showed the presence of urea and imidazole. This reaction was repeated with *N*-methylurea, *N,N'*-dimethylurea and *N,N*-dimethylurea, over 92% of the starting materials was recovered in all cases.

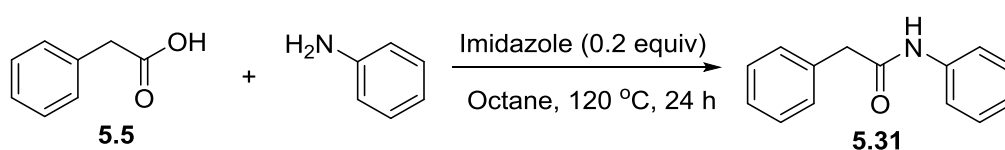


Figure 5.24: Reaction with aniline

To investigate further the degradation theory, phenylacetic acid (**5.5**) was exposed to the reaction conditions with aniline as the nitrogen source instead of *N,N'*-diphenylurea (**Figure 5.24**). The reaction was carried out with and without the catalyst present and conversions to **5.31** of 70% and 71% were observed, respectively. As the conversions are effectively the same, this would suggest the catalyst played no role in this reaction. These conversions are considerably higher than those observed when the reaction was carried out with *N,N'*-diphenylurea where a conversion of 42 % was observed.

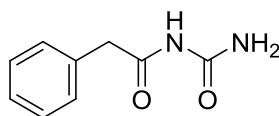
These pieces of evidence would suggest that the reaction does not proceed *via* the degradation of urea, as no degradation of urea was observed under the reaction conditions and a considerably higher conversion was seen when aniline was used as the nitrogen source compared with *N,N'*-diphenylurea. As both these results are not consistent with the observed reactivity, there is no evidence to support the degradation theory.

5.3.8.2 Formation of *N*-acylurea intermediate

The second possible reaction route is through the formation of an *N*-acylurea intermediate (**Figure 5.23**, equation 2). The intermediate could form through the nucleophilic attack of an urea nitrogen on the electrophilic centre of the acid,

resulting in the loss of water. The water molecule could attack the urea electrophilic centre resulting in the hydrolysis of the N-C bond, to give the amide product and the carbamic acid byproduct. Carbamic acid is unstable and readily degrades to carbon dioxide and ammonia, as both of these are gases they would readily leave the reaction mixture, acting as a driving force in the reaction.

The plausibility of the proposed intermediates was further investigated, by determining if the intermediate is present in the reaction and exploring the decomposition of the *N*-acylurea intermediate.

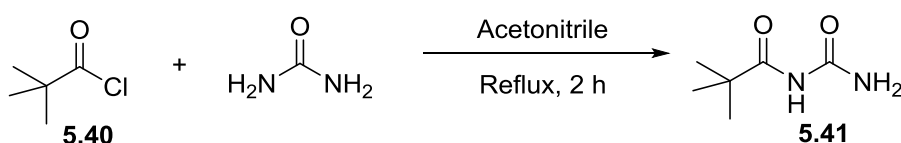


5.39

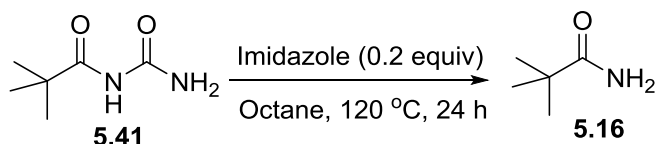
Figure 5.25: Possible reaction intermediate

The reaction between phenylacetic acid and urea under optimised condition was conducted, but only allowed to run for six hours. HRMS analysis was run on the crude reaction mixture, to determine if any of the phenylacetylurea (**5.39**) intermediate was present (**Figure 5.25**). An m/z of 201.0636 was found, which corresponds with the sodium adduct of the intermediate, expected m/z of 201.0640.

An *N*-acylurea was synthesised from trimethylacetyl chloride (**5.40**), following the procedure reported by Kaufmann *et al.* (**Figure 5.26**).¹⁵⁶

Figure 5.26: Synthesis of *N*-acylurea intermediate

N-Carbamoylpivalamide (**5.41**) was then subjected to different reaction conditions to determine if it was a possible intermediate in the reaction.

Table 5.13: Formation of amide from *N*-carbamoylpivalamide

entry	Catalyst	Water	Conversion (%) ^[a]
1	Yes	No	4
2	No	No	2
3	Yes	Yes	14
4	No	Yes	4

N-Carbamoylpivalamide (1 mmol), water (1 mmol) and imidazole (0.2 mmol) in octane (1 mL) at 120 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

The reactions were run with and without the catalyst, as well as with and without water. The addition of water was to simulate the production of water in the formation of the *N*-acylurea intermediate in the reaction between the acid and urea. When the *N*-acylurea was subject to optimised reaction conditions without the presence of the catalyst or water, only a 2% conversion to the amide product was observed (**Table 5.13**, entry 2). When the reaction was run in the presence of one equivalent of water but no catalyst, a conversion of 4% to the amide was gained (**Table 5.13**, entry 4). Similarly when the reaction was run with catalyst but no water a 4% conversion was observed (**Table 5.13**, entry 1). When both catalyst and water was added to the reaction, a conversion of 14% was seen to the corresponding amide (**Table 5.13**, entry 3).

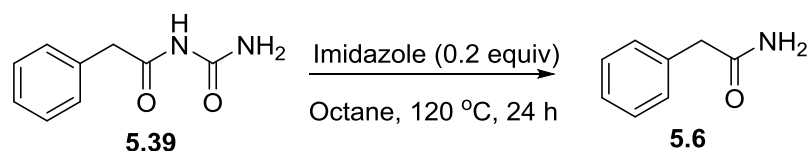
Using the same method as above, phenylacetylurea (**5.39**) was also synthesised to investigate the decomposition of a possible intermediate (**Figure 5.27**).



Figure 5.27: Synthesis of phenylacetylurea

Phenylacetylurea (**5.39**) was subjected to the same conditions as above, to see if the same trends were observed.

Table 5.14: Formation of amides from phenylacetylurea



Entry	Catalyst	Water	Conversion (%) ^[a]	Conversion (%) ^{[a][b]}
1	Yes	No	0	4
2	No	No	22	0
3	Yes	Yes	0	8
4	No	Yes	13	0

Phenylacetylurea (0.5 mmol), water (0.5 mmol) and imidazole (0.1 mmol) in octane (0.5 mL) at 120 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra. ^[b] Hydrocinnamic acid (0.5 mmol) added.

Interestingly the opposite trend was observed, no formation of phenylacetamide (**5.6**) was observed for the reactions with the catalyst present (Table 5.14, entries 1 and 3). Without imidazole present, the reaction with water present gave a conversion of 13% (Table 5.14, entry 4), whereas the reaction with just phenylacetylurea gave a slightly higher conversion of 22% (Table 5.14, entry 2).

It was thought that the carboxylic acid may play some role in the catalysis, apart from its role as the starting material. The reactions with phenylacetylurea (**5.39**) were repeated with the addition of hydrocinnamic acid, to determine if the acid needed to be present. Hydrocinnamic acid was chosen instead of phenylacetic acid, to ensure the ¹H NMR spectra could easily be interpreted as there is no overlap in their peaks, and there would be no confusion if the acid reacted as well as the *N*-acylurea.

The reaction without catalyst present showed no formation of the amide product (Table 5.14, entries 2 and 4). Whereas the reaction with both imidazole and water gave a conversion of 8% (Table 5.14, entry 3) and the reaction with just imidazole and no water gave 4% of amide **5.6** (Table 5.14, entry 1).

Although these results are in better agreement with the result gained for *N*-carbamoylepivalamide (**4.41**), in both cases the conversion into amide are very low compared with those achieved in between a carboxylic acid and urea. If the reaction was proceeding *via* the *N*-acylurea intermediate, a conversion similar to that seen in

the reaction with a carboxylic acid would be expected. While the mass ion of the sodium adduct of the intermediate **5.39** was found by HRMS, it was found with an intensity of only 3%, suggesting very little was present. From these results we can determine it is unlikely that the reaction is proceeding *via* an *N*-acylurea intermediate and a more complicated mechanism is taking place than we originally envisioned.

5.3.8.3 Mode of activation

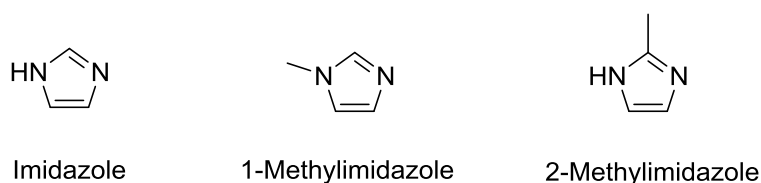
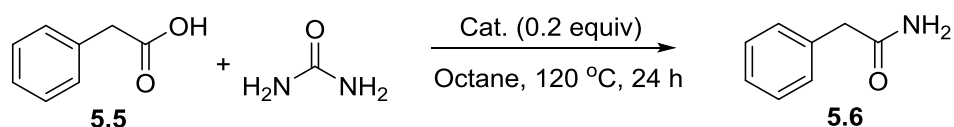


Figure 5.28: Alternative imidazole catalysts

To investigate how the imidazole was acting as a catalyst, 1-methylimidazole and 2-methylimidazole (**Figure 5.28**) were used in place of imidazole as the catalyst in the reaction. This could determine if the presence of the methyl group disrupts the catalytic activity.

Table 5.15: Functionalised imidazole catalytic activity



Entry	Catalyst	Conversion (%) ^[a]
1	Background	24
2	Imidazole	86
3	1-Methylimidazole	66
4	2-Methylimidazole	37
5	DMAP	84

Phenylacetic acid (1 mmol), urea (1 mmol) and catalyst (0.2 mmol) in octane (1 mL) at 110 °C for 24 h. ^[a] Conversions determined by analysis of ¹H NMR spectra.

There is a significant decrease in conversion compared with imidazole when the methyl group is positioned in the 2 position, between the two nitrogens (**Table 5.15**, entry 4), from 86 % to 37 %. Whereas there is only a small decrease in conversion compared with imidazole, 86% to 66%, when the methyl group is

positioned on one of the nitrogens (**Table 5.15**, entry 3). These results suggest the mode of activation is through the lone pair of electrons on the imine nitrogen. This would explain the sharp decrease in conversion for 2-methylimidazole, as the methyl group is sterically blocking the lone pair, compared with 1-methylimidazole, where the methyl group is further away from the imine and therefore leaving the lone pair open to react.

This is further supported by the similar catalytic activity shown by DMAP (**Table 5.15**, entry 5), as DMAP also has an sp^2 nitrogen which could react through its lone pair of electrons.

The mechanism by which the reaction proceeds is still unclear and due to time constraints could not be explored further at this time.

5.4 Conclusion

A successful catalyst system was developed for the transformation of unactivated carboxylic acids to primary amides catalysed by imidazole with urea as the nitrogen source. It should be noted that DMAP also showed promising catalytic activity in this reaction. The reaction was demonstrated to work for a range of substrates with moderate to excellent yields. It was also demonstrated that secondary amides could be synthesised from unactivated carboxylic acids, when urea is substituted for *N,N*-dimethylurea and 1,3-diphenylurea to produce *N*-methyl and *N*-phenyl amides, respectively. While some work was carried out to investigate possible mechanisms, results are so far inconclusive.

5.5 Future work

As mentioned in the conclusion, the mechanism of the reaction is still unknown. It is thought that the reaction may be further optimised if the mechanism is known. It was initially thought that imidazole promoted the reaction by activating one of the starting materials or that it stabilised an intermediate. The investigations carried out so far suggest that the mechanism may be more complicated than originally thought. The mechanism could be further explored by carrying out kinetic studies, these might help determine what role the starting materials play and the order of the reaction with respect to each element of the reaction.

Binding studies could also be carried out between the different elements of the reaction, to determine if imidazole binds to the acid or urea. This could be achieved through ^1H NMR studies, by running ^1H NMR experiments at the reaction temperature with either urea or an acid and increasing amounts of imidazole. By analysis of these ^1H NMR spectra any changes in chemical shift would indicate that some interactions were taking place between imidazole and the reagents.

By gathering these sets of data a better understanding of the mechanism may be gained.

6 Experimental

6.1 General experimental

All reactions were performed under an argon or nitrogen atmosphere using starting materials and solvents obtained from commercial sources without further purification. Chemicals were purchased from Acros Organics, Sigma-Aldrich, Alfa Aesar and Fluka. Dry solvents were obtained from an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to petroleum ether boiling at 40-60 °C.

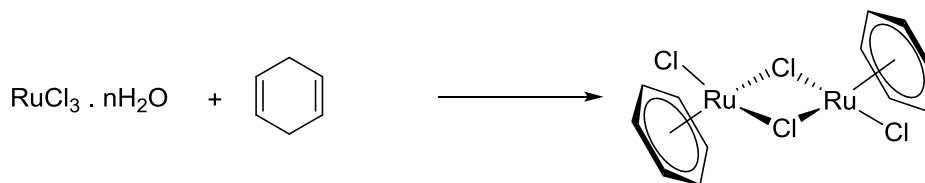
^1H and ^{13}C NMR spectra were recorded on a Brüker Advance 250 MHz, a Brüker Advance 300 MHz or an Agilent 500 MHz spectrometer at 303K. The spectra were recorded in CDCl_3 , DMSO-D_6 or $(\text{CD}_3)_2\text{CO}$ solutions with chemical shifts reported relative to the residual CDCl_3 , DMSO-D_6 or $(\text{CD}_3)_2\text{CO}$ as an internal standard, respectively. Chemical shift is reported in parts per million (ppm) and all coupling constants, J , are reported in Hertz (Hz). The multiplicity of the signals is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; dsept, doublet of septets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; dtd, doublet of triplet of doublets; ddq, doublet of doublet of quartets; td, triplet of doublets; tt, triplet of triplets; tq, triplet of quartets; qd, quartet of doublets; quin, quintet; sex, sextet; hep, heptet.

Thin layer chromatography was performed using aluminium backed plates coated with Merck Kieselgel 60 GF₂₅₄ or Macherey-Nagel SilG/UV_{254 nm} silica gel. Plates were visualised under UV light (254 nm) and stained with phosphomolybdic acid followed by heating. Normal phase flash silica column chromatography was performed using Fisher 60 Å silica gel (35-70 µm).

Mass spectra were recorded using an electrospray Time-of-Flight MicroTOFTM mass spectrometer. Masses were recorded in either positive or negative mode. Samples were introduced as either flow injection or syringe pump. Samples were diluted with HPLC grade methanol.

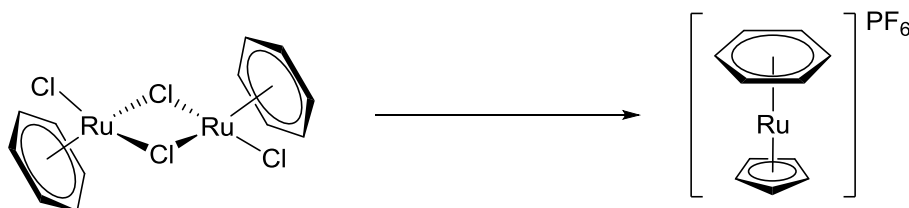
6.2 Experimental procedure: Chapter 3

Synthesis of $[(\eta^6\text{-benzene})\text{RuCl}_2]_2$ 3.2:⁹⁵



Ruthenium (III) chloride hydrate 35-40% (3 g) and 1,4-cyclohexadiene (7.5 mL, 6.4 g, 79.4 mmol) in methanol (150 mL) in a Schlenk tube under an N_2 atmosphere were heated to reflux at 80 °C for 5 hours. The reaction was allowed to cool to room temperature, filtered and washed with methanol and dried to give a brown powder as the product (2.57 g, 89.2% yield). ^1H NMR (250 MHz, DMSO) δ 5.96 (s, 6H, C_6H_6); ^{13}C NMR (75 MHz, DMSO) δ 87.7.

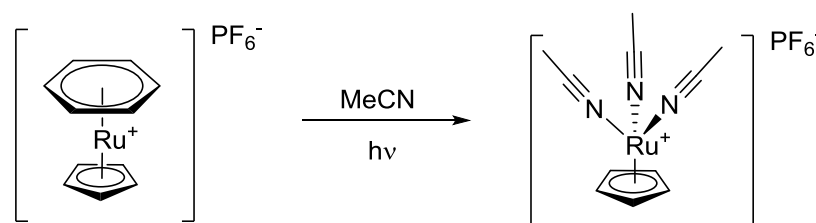
Synthesis of $[\text{RuCp}(\eta^6\text{-benzene})]\text{PF}_6$ 3.3:⁹⁵



Cyclopentadiene (CpH) was freshly cracked by distillation of dicyclopentadiene at 177 °C, the freshly cracked CpH was stored at 0 °C to prevent dimerization. Potassium carbonate (4.3 g, 30.8 mmol) was placed in a Schlenk tube under an N_2 atmosphere and dried with a heat gun under vacuum, the tube was then cooled following standard Schlenk procedure. $[\text{RuCl}_2(\eta^6\text{-benzene})]_2$ (2.6 g, 5.14 mmol) was added followed by ethanol (100 mL, dried over molecular sieves and degassed by bubbling through with N_2 for 30 mins.). Freshly cracked CpH (7.8 mL, 6.1 g, 92.48 mmol) was then added and the reaction heated to 60 °C for 18 hours. The reaction was allowed to cool and filtered through a celite plug; the celite was washed with 20 mL of ethanol. The filtrate was concentrated to ~10 mL *in vacuo* and a solution of ammonium hexafluorophosphate (3.35 g, 20.56 mmol) in water (33.5 mL) was added, a tan precipitate formed on addition. The remaining ethanol was removed *in vacuo*. The water suspension was cooled for 2 hours, the precipitate was collected by filtration followed by washing with water and this was dried under vacuum to

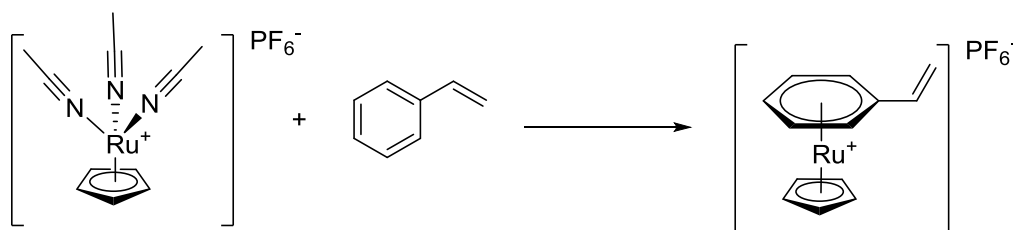
give a tan powder. The powder was dissolved in the minimum amount of acetone, diethyl ether was added slowly until the formation of a tan precipitate was no longer observed. The suspension was cooled for 2 hours, the precipitate was collected by filtration followed by washing with diethyl ether and dried under vacuum to give the product as an off white powder (3.15 g, 79% yield). ^1H NMR (250 MHz, $(\text{CD}_3)_2\text{CO}$) δ 6.34 (s, 6H, C_6H_6), 5.54 (s, 5H, C_5H_5); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$) δ 87.1, 81.3; ^{19}F NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ -72.72 (d, J = 710 Hz, PF_6^-). HRMS calcd for $\text{C}_{11}\text{H}_{11}\text{Ru}^+$: 244.9904; Found: 244.9909.

Synthesis of $[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ 3.4:⁹⁵



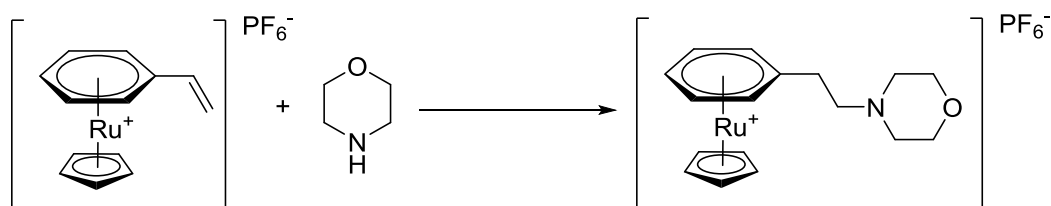
$[\text{RuCp}(\eta^6\text{-Benzene})]\text{PF}_6$ (50 mg, 0.12 mmol) was placed in degassed acetonitrile (20 mL) (degassed by bubbling through with N_2 for 30 min) in a Schlenk tube under an N_2 atmosphere. The solution was irradiated with 400 W medium pressure mercury lamp for 16 hours. The solvent was removed *in vacuo*. NMR showed complete conversion into the product as a dark brown powder (53 mg, 98 % yield) ^1H NMR (250 MHz, $(\text{CD}_3)_2\text{CO}$) δ 4.26 (s, 5H, C_5H_5), 2.44 (s, 9H, CH_3CN); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$) δ 126.8, 69.5, 3.2.

Synthesis of $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$ 3.6:



$[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (500 mg, 1.15 mmol) and styrene (397 μL , 359.3 mg, 3.45 mmol) were placed in degassed DCE (60 mL) (degassed by three freeze-thaw cycles) in a

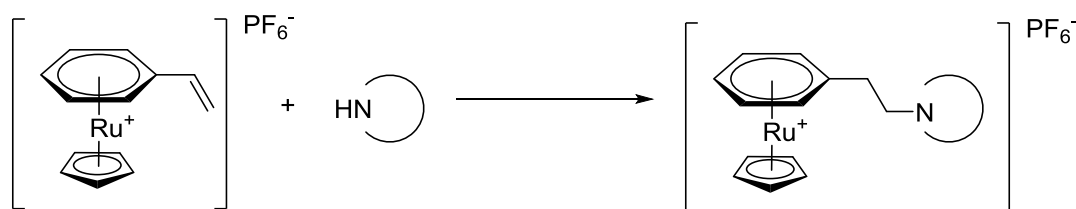
Schlenk tube under an N₂ atmosphere, the reaction was then heated to 80 °C for 24 hours. The reaction was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction was left under high vacuum for 30 min to remove excess styrene. The product was recrystallised by dissolving the reaction mixture in the minimum amount of DCM followed by the slow addition of diethyl ether, which afforded a cream precipitate, which was collected to give the product. A residue remained in the flask, the above recrystallisation was repeated until no further precipitate formed. The precipitates were combined to give the product as a cream powder (321 mg, 68% yield). ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.65 (dd, J= 17.5 Hz and 10.8 Hz, 1H, PhHC=CH₂), 6.57 (d, J = 5.8 Hz, 2H, C₆H₅), 6.37 (t, J = 5.7 Hz, 2H, C₆H₅), 6.29 (t, J=5.7 Hz, 1H, C₆H₅), 6.07 (d, J = 17.5 Hz, 1H, HC=CH₂), 5.57 (d, J =10.8 Hz, 1H, C=CH₂), 5.46 (s, 5H, C₅H₅); ¹³C NMR (75 MHz, (CD₃)₂CO) δ 133.4, 121.6, 100.7, 86.8, 86.5, 84.9, 82.0; ¹⁹F NMR (500 MHz, (CD₃)₂CO) δ -72.58 (d, J= 707 Hz, PF₆). HRMS calcd for C₁₃H₁₃Ru⁺:271.0055; Found: 271.0066.

Nucleophilic addition solvent and temperature screen:

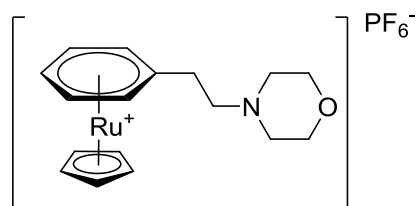
[RuCp(η^6 -Styrene)]PF₆ (5 mg, 0.012 mmol) and morpholine (1.6 μ L, 1.57 mg, 0.018 mmol) in a solvent (0.2 mL) were heated under the following conditions:

Solvent	20 °C Conversion ^[a] (%)	40 °C Conversion ^[a] (%)	60 °C Conversion ^[a] (%)
THF	nr	nr	50% (6 h) 100% (24 h)
DCE	nr	nr	71% (6 h)
Toluene	nr	nr	nr
Acetonitrile	nr	nr	67% (6 h)
DCM	nr	57% (24 hr)	-
Diethyl ether	nr	nr	nr

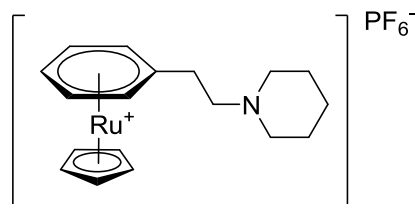
The reactions were monitored by TLC. ^[a] Conversion determined by analysis of ¹H NMR spectra by comparison of integration of Cp peaks at 5.53 (s, 5H, C₅H₅, product) and 5.50 (s, 5H, C₅H₅, starting material).

General procedure 3.1:

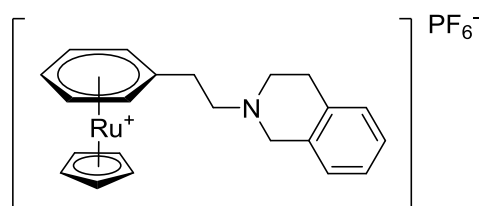
[RuCp(η^6 -Styrene)]PF₆ (10 mg, 0.024 mmol) and amine (0.036 mmol) in THF (0.5 mL) were heated at 60 °C for 24 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo*. As these experiments were feasibility studies, the products were not isolated, ¹H NMR data was taken from crude reaction mixture.

Synthesis of [RuCp(η^6 -4-phenethylmorpholine)]PF₆ 3.8:

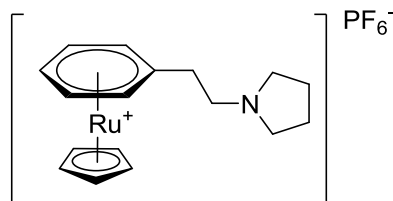
Following the general procedure 3.1, [RuCp(η^6 -styrene)]PF₆ (10 mg, 0.024 mmol) and morpholine (3.2 μ L, 3.1 mg, 0.036 mmol) were heated at 60 °C for 24 hours, 100% conversion determined by analysis of ¹H NMR spectra. Crude ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.43-6.40 (m, 2H, C₆H₅), 6.31-6.26 (m, 3H, C₆H₅), 5.50 (s, 5H, C₅H₅), 3.59 (t, J = 5.6 Hz, 4H, O(CH₂)₂), 2.80 (t, J = 6.3 Hz, 2H, PhCH₂CH₂), 2.63 (t, J = 6.3 Hz, 2H, PhCH₂CH₂), 2.45 (t, J = 5.6 Hz, 4H, N(CH₂)₂); HRMS calcd for C₁₇H₂₂NORu⁺: 358.0739; Found: 358.0777.

Synthesis of [RuCp(η^6 -1-phenethylpiperidine)]PF₆ 3.8:

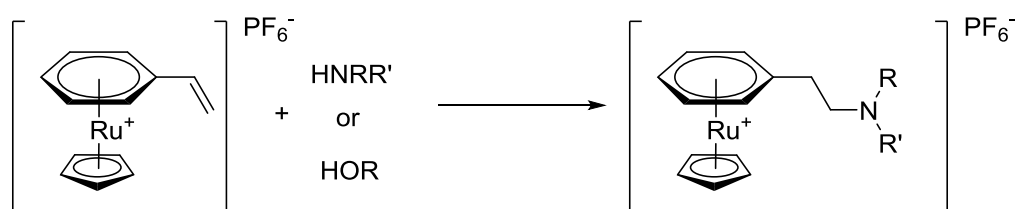
Following the general procedure 3.1, [RuCp(η^6 -styrene)]PF₆ (10 mg, 0.024 mmol) and piperidine (3.6 μ L, 3.1 mg, 0.036 mmol) were heated at 60 °C for 24 hours, 100% conversion determined by analysis of ¹H NMR spectra. Crude ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.41-6.39 (m, 2H, C₆H₅), 6.31-6.27 (m, 3H, C₆H₅), 5.51 (s, 5H, C₅H₅), 2.75 (t, J = 6.6 Hz, 2H, PhCH₂CH₂), 2.57 (t, J = 6.6 Hz, 2H, PhCH₂CH₂), 2.40 (br s, 4H, N(CH₂)₂), 1.52 (br s, 4H, CCH₂C), 1.4 (br s, 2H, CCH₂C); HRMS calcd for C₁₈H₂₄NRu⁺: 356.0947; Found: 356.0995.

Synthesis of [RuCp(η^6 -2-phenethyl-1,2,3,4-tetrahydroisoquinoline)]PF₆ 3.9:

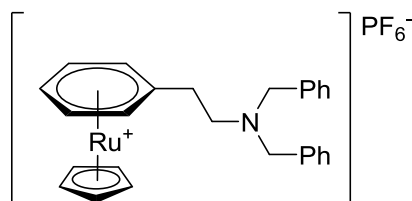
Following the general procedure 3.1, [RuCp(η^6 -styrene)]PF₆ (10 mg, 0.024 mmol) and 1,2,3,4-tetrahydroisoquinoline (4.5 μ L, 4.8 mg, 0.036 mmol) were heated at 60 °C for 24 hours, 100% conversion determined by analysis of ¹H NMR spectra. Crude ¹H NMR (250 MHz, (CD₃)₂CO) δ 7.12-6.96 (m, 4H, C₆H₄), 6.45-6.43 (m, 2H, C₆H₅), 6.28-6.24 (m, 3H, C₆H₅), 5.49 (s, 5H, C₅H₅), 3.65 (s, 2H, NCH₂C), 2.91-2.77 (m, 8H, PhCH₂CH₂, NCH₂CH₂C); HRMS calcd for C₂₂H₂₄NRu⁺:404.0947: Found:404.0983.

Synthesis of [RuCp(η^6 -1-phenethylpyrrolidine)]PF₆ 3.10:

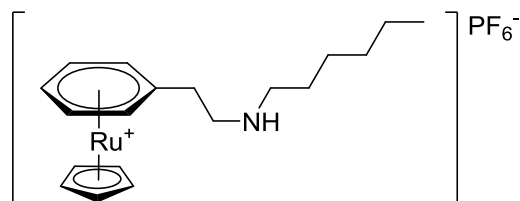
Following the general procedure 3.1, [RuCp(η^6 -styrene)]PF₆ (10 mg, 0.024 mmol) and pyrrolidine (4.9 μ L, 2.6 mg, 0.036 mmol) were heated at 60 °C for 24 hours, 100% conversion determined by analysis of ¹H NMR spectra. Crude ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.43-6.41 (m, 2H, C₆H₅), 6.29-6.27 (m, 3H, C₆H₅), 5.51 (s, 5H, C₅H₅), 2.79-2.73 (m, 4H, PhCH₂CH₂), 2.4 (br s, 4H, N(CH₂)₂), 1.71 (br s, 4H, CCH₂CH₂C); HRMS calcd for C₁₇H₂₂NRu⁺:342.0790: Found: 342.0855.

General procedure 3.2:

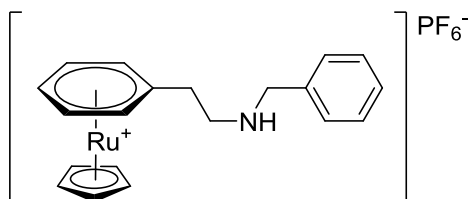
$[\text{RuCp}(\eta^6\text{-Styrene})]\text{PF}_6$ (10 mg, 0.024 mmol) and amine/alcohol (0.036 mmol) in a THF (0.5 mL) were heated at 80 °C for 24 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo*. As these experiments were feasibility studies, the products were not isolated, ^1H NMR data was taken from crude reaction mixture.

Synthesis of $[\text{RuCp}(\eta^6\text{-}N,N\text{-dibenzyl-2-phenylethan-1-amine})]\text{PF}_6$ 3.12:

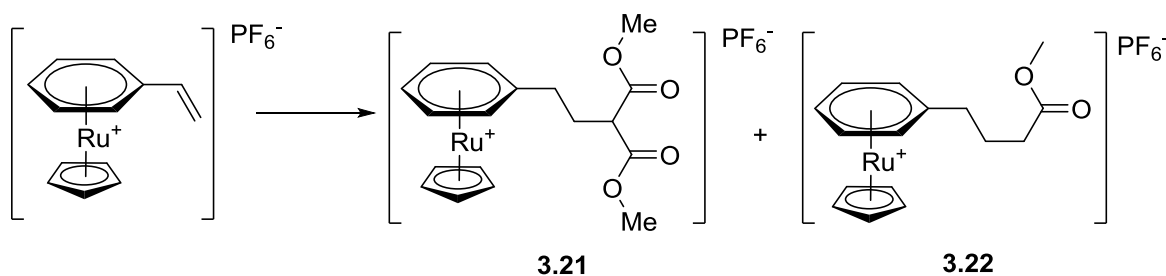
Following the general procedure 3.2, $[\text{RuCp}(\eta^6\text{-styrene})]\text{PF}_6$ (10 mg, 0.024 mmol) and dibenzylamine (6.9 μL , 7.1 mg, 0.036 mmol) in THF gave 21% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of integration of Cp peak in starting material and product. by comparison of integration of Cp peaks at 5.53 (s, 5H, C_5H_5 , product) and 5.50 (s, 5H, C_5H_5 , starting material)

Synthesis of [RuCp(η^6 -N-phenethylhexan-1-amine)]PF₆ 3.14:

Following the general procedure 3.2, [RuCp(η^6 -styrene)]PF₆ (10 mg, 0.024 mmol) and hexylamine (4.8 μ L, 3.6 mg, 0.036 mmol) were heated at 80 °C for 24 hours, 53% conversion determined by analysis of ¹H NMR spectra by comparison of integration of Cp peak in starting material and product. Crude ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.43-6.40 (m, 2H, C₆H₅), 6.29-6.25 (m, 3H, C₆H₅), 5.50 (s, 5H, C₅H₅), 2.90 (t, J = 6.9 Hz, 2H, PhCH₂CH₂), 2.73 (br s, 2H, NCH₂CH₂), 2.59 (t, J = 6.9 Hz, 2H, CH₂CH₂) 1.46-1.41 (m, 2H, CH₂CH₂CH₂) 1.28-1.27 (m, 6H, CH₂CH₂CH₂CH₂CH₂) 0.89-0.84 (m, 3H, CH₂CH₃); HRMS calcd for C₁₈H₂₈NRu⁺: 372.1260 : Found: 372.1276.

Synthesis of [RuCp(η^6 -N-benzyl-2-phenylethanamine)]PF₆ 3.16:

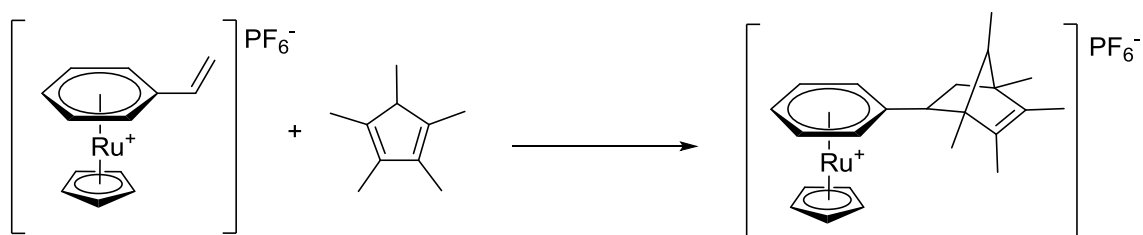
Following the general procedure 3.2, [RuCp(η^6 -styrene)]PF₆ (10 mg, 0.024 mmol) and benzylamine (3.9 μ L, 3.9 mg, 0.036 mmol) were heated at 80 °C for 24 hours, 71% conversion determined by analysis of ¹H NMR spectra by comparison of integration of Cp peak in starting material and product. Crude ¹H NMR (250 MHz, (CD₃)₂CO) δ 7.36-7.19 (m, 5 H, C₆H₅), 6.42-6.39 (m, 2H, C₆H₅), 6.28-6.22 (m, 3H, C₆H₅), 5.48 (s, 5H, C₅H₅), 3.78 (s, 2H, NCH₂Ph) 2.81 (t, J = 6.3 Hz, 2H, PhCH₂CH₂), 2.75 (t, J = 6.3 Hz, 2H, CH₂CH₂NH); HRMS calcd for C₂₀H₂₂NRu⁺: 378.0790: Found: 378.0777.

Synthesis of [RuCp(η^6 -dimethyl-2-phenethylmalonate)]PF₆ 3.21:

[RuCp(η^6 -Styrene)]PF₆ (10 mg, 0.024 mmol), dimethylmalonate (6.5 μ L, 6.3 mg, 0.048 mmol) and sodium methoxide (2.6 mg, 0.048 mmol) in a THF (0.5 mL) were heated at 80 °C for 24 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo*. 100% Conversion calculated by analysis of crude ¹H NMR spectra to 2 products, a and b.

3.21: ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.42-6.28 (m, 5H, C₆H₅), 5.53 (s, 5H, C₅H₅), 3.71 (s, 6H, OCH₃), 3.57 (t, J = 7.3 Hz, 1H, CH₂CH), 2.72-2.60 (m, 4H, PhCH₂CH₂CH); HRMS calcd for C₂₀H₂₂NRu⁺: 403.0478; Found: 403.0544.

3.22: ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.42-6.28 (m, 5H, C₆H₅), 5.52 (s, 5H, C₅H₅), 3.76 (s, 3H, OCH₃), 2.72-2.60 (m, 4H, PhCH₂CH₂CH) 2.34-2.26 (m, 2H, CH₂CH₂C); HRMS calcd for C₂₀H₂₂NRu⁺: 345.0423; Found: 345.0442.

Diels–Alder conditions screen: synthesis of [RuCp(η^6 -1,2,3,4,7-pentamethyl-5-phenylbicyclo[2.2.1]hept-2-ene)]PF₆ 3.23:

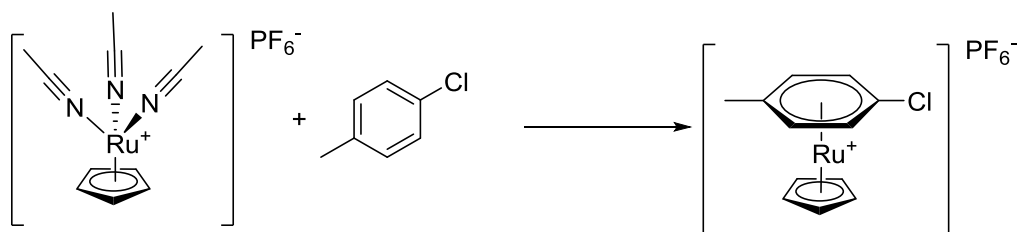
[RuCp(η^6 -Styrene)]PF₆ (10 mg, 0.024 mmol) and 1,2,3,4,5-pentamethylcyclopentadiene (see table) in a solvent (0.5 mL) were heated at T °C for 24 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo*.

Entry	Solvent	Diene (μL)	Diene (mg)	Diene (mmol)	Temp. ($^{\circ}\text{C}$)	Conv. ^[a] (%)
1	THF	5.6	4.9	0.036	60	46
2	THF	5.6	4.9	0.036	80	83
3	DCE	5.6	4.9	0.036	80	85
4	DCE	5.6	4.9	0.036	85	91
5	DCE	6.4	5.6	0.041	85	83
6	DEC	7.5	6.5	0.045	85	87

^[a] Conversion determined by analysis of ^1H NMR spectra by comparison of integration of Cp peaks at 5.47 (s, 5H, C_5H_5 , product) and 5.49 (s, 5H, C_5H_5 , starting material).

As these experiments were feasibility studies, the products were not isolated, ^1H NMR data was taken from the crude reaction. Crude ^1H NMR (250 MHz, $(\text{CD}_3)_2\text{CO}$) δ 6.29-6.25 (m, 5H, C_6H_5), 5.47 (s, 5H, C_5H_5), further characterisation not carried out; HRMS calcd for $\text{C}_{20}\text{H}_{22}\text{NRu}^+$: 407.1307; Found: 407.1387.

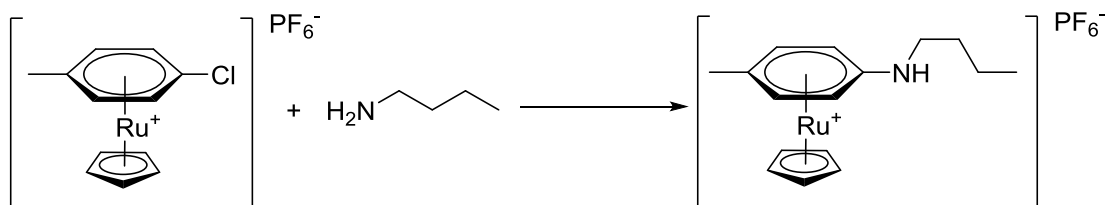
Synthesis of $[\text{RuCp}(\eta^6\text{-4-chlorotoluene})]\text{PF}_6$ 3.24:



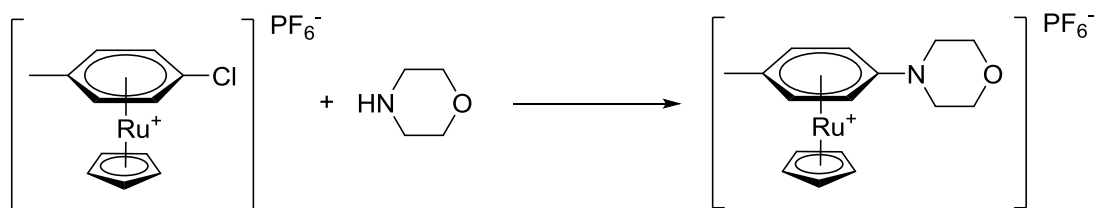
$[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (250 mg, 0.57 mmol) and 4-chlorotoluene (204 μL , 217.7 mg, 1.72 mmol) were placed in degassed 1,2-dichloroethane (30 mL) (degassed by three freeze-thaw cycles) in a Schlenk tube under an N_2 atmosphere, the reaction was then heated to $80\text{ }^{\circ}\text{C}$ for 24 hours. The reaction was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction was left under high vacuum for 30 mins to remove excess 4-chlorotoluene. The product was recrystallised by dissolving the reaction mixture in the minimum amount of DCM followed by the slow addition of diethyl ether, which afforded a brown precipitate which was collected to give the product. A residue remained in the flask, the above recrystallisation was repeated until no further precipitate formed. The precipitates

were combined to give the product as a brown powder (205 mg, 77% yield). ^1H NMR (250 MHz, $(\text{CD}_3)_2\text{CO}$) δ 6.76 (d, J = 6.3 Hz, 2H, C_6H_4), 6.50 (d, J = 6.3 Hz, 2H, C_6H_4), 5.46 (s, 5H, C_5H_5), 2.40 (s, 3H, PhCH_3); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$) δ 87.1, 84.5, 81.4, 81.3, 79.4, 69.4, 30.2; ^{19}F NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ -72.43 (d, J = 708 Hz, PF_6). HRMS calcd for $\text{C}_{12}\text{H}_{12}\text{Ru}^+$: 292.9666; Found: 292.9689.

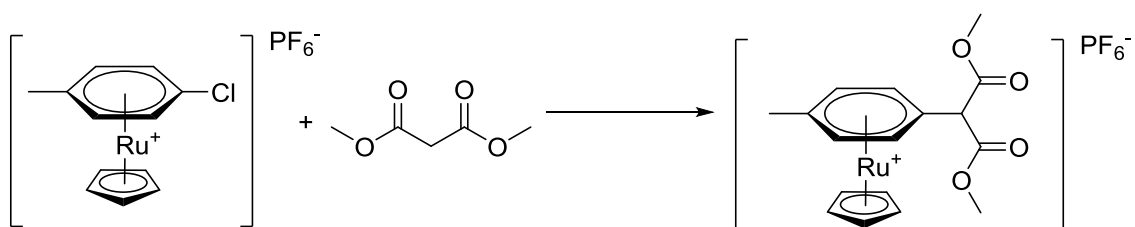
Synthesis of $[\text{RuCp}(\eta^6\text{-N-butylaniline})]\text{PF}_6$ 3.25:



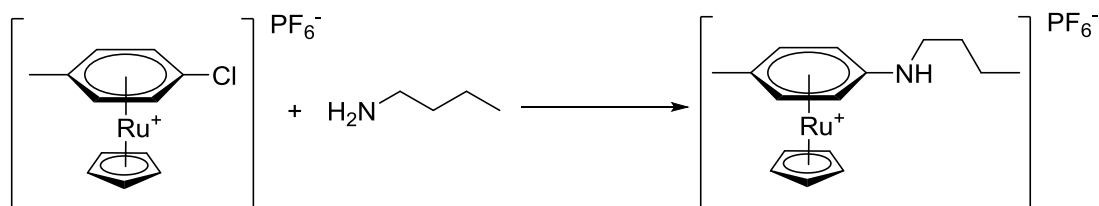
$[\text{RuCp}(\eta^6\text{-4-Chlorotoluene})]\text{PF}_6$ (10 mg, 0.023 mmol), butylamine (22.7 μL , 16.8 mg, 0.23 mmol) and acetic acid (26.3 μL , 27.6 mg, 0.46 mmol) in THF (0.5 mL) were heated to 80 $^\circ\text{C}$ for 24 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo*. 93% Conversion determined by analysis of ^1H NMR spectra by comparison of integration of Cp peak in starting material and product. Crude ^1H NMR (250 MHz, $(\text{CD}_3)_2\text{CO}$) δ 6.05-6.02 (d, J = 6.6 Hz, 2H, C_6H_4), 5.92-5.89 (d, J = 6.6 Hz, 2H, C_6H_4), 5.27 (s, 5H, C_5H_5), 3.39 (t, J = 7 Hz, 2H, NCH_2CH_2), 2.26 (s, 3H, PhCH_3), 1.70-1.59 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.44-1.32 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.95-0.88 (m, 3H, CH_2CH_3); HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{Ru}^+$: 330.0796; Found: 330.0817.

Synthesis of [RuCp(η^6 -4-phenylmorpholine)]PF₆ 3.26:

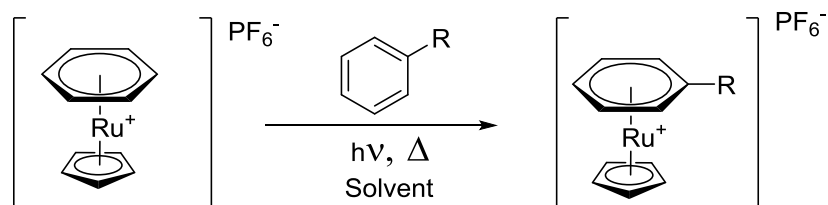
[RuCp(η^6 -4-Chlorotoluene)]PF₆ (10 mg, 0.023 mmol), morpholine (4.4 μ L, 4.0 mg, 0.046 mmol) and acetic acid (2.6 μ L, 2.8 mg, 0.046 mmol) in a THF (0.5 mL) were heated to 80 °C for 16 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo*. 48% Conversion determined by analysis of ¹H NMR spectra by comparison of integration of Cp peak in starting material and product. Crude ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.15 (d, *J* = 6.8 Hz, 2H, C₆H₄), 6.06 (d, *J* = 6.8 Hz, 2H, C₆H₄), 5.47 (s, 5H, C₅H₅), 3.78 (t, *J* = 5 Hz, 2H, CH₂CH₂O), 3.08 (t, *J* = 5 Hz, 2H NCH₂CH₂), 2.35 (s, 3H, ArCH₃); HRMS calcd for C₁₃H₁₃Ru⁺: 344.0583; Found: 344.0599.

Synthesis of [RuCp(η^6 -dimethyl 2-phenylmalonate)]PF₆ 3.27:

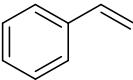
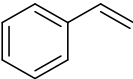
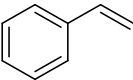
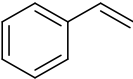
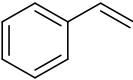
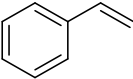
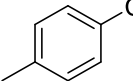
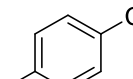
[RuCp(η^6 -4-Chlorotoluene)]PF₆ (10 mg, 0.023 mmol), dimethyl malonate (5.3 μ L, 6.1 mg, 0.046 mmol) and sodium methoxide (2.5 mg, 0.046 mmol) in a THF (0.5 mL) were heated to 80 °C for 16 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo*. Conversion not determined from ¹H NMR spectra, but mass ion found. HRMS calcd for C₁₃H₁₃Ru⁺: 389.0321; Found: 389.0328.

Synthesis of [RuCp(η^6 - N-butylaniline)]PF₆ 3.25:

[RuCp(η^6 -4-Chlorotoluene)]PF₆ (10 mg, 0.023 mmol) and butylamine (22.7 μ L, 16.8 mg, 0.23 mmol) in a THF (0.5 mL) were heated to 80 °C for 24 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo*. 39% Conversion determined by analysis of ¹H NMR spectra by comparison of integration of Cp peak in starting material and product. Crude ¹H NMR (250 MHz, (CD₃)₂CO) δ 6.05-6.02 (d, J = 6.6 Hz, 2H, C₆H₄), 5.92-5.89 (d, J = 6.6 Hz, 2H, C₆H₄), 5.27 (s, 5H, C₅H₅), 3.39 (t, J = 7 Hz, 2H, NCH₂CH₂), 2.26 (s, 3H, PhCH₃), 1.70-1.59 (m, 2H, CH₂CH₂CH₂), 1.44-1.32 (m, 2H, CH₂CH₂CH₃), 0.95-0.88 (m, 3H, CH₂CH₃); HRMS calcd for C₁₃H₁₃Ru⁺: 330.0796; Found: 330.0817.

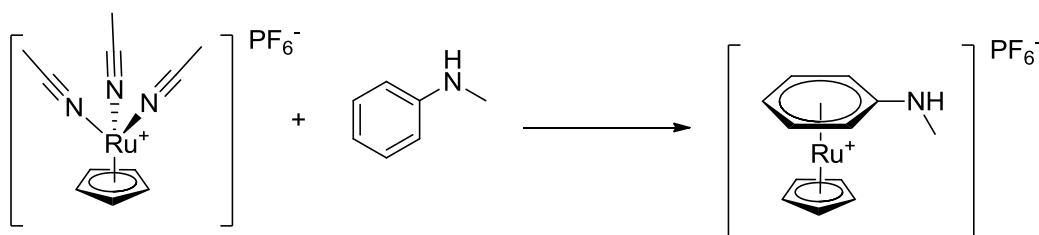
Arene exchange reactions 3.6/3.24:

[RuCp(η^6 -Benzene)]PF₆ (10 mg, 0.024 mmol) and arene (see table) were placed in degassed acetonitrile:solvent (0.5:0.5 mL) (degassed by bubbling N₂ through for 30 min) in a Schlenk tube under an N₂ atmosphere, the reaction was then heated (see table) and irradiated with a 400 W mercury medium pressure lamp for 16 hours. The reaction was allowed to cool and the solvent removed *in vacuo*.

Entry	Solvent	Temp (°C)	Arene	μL	Mg	mmol	Conv. ^[a] (%)
1	Acetonitrile	60		8.8	7.97	0.077	-
2	DCE	60		8.8	7.97	0.077	25
3	THF	60		8.8	7.97	0.077	30
4	THF	60		58.4	53.4	0.52	47
5	DCE	60		58.4	53.4	0.52	45
6	THF	80		58.4	53.4	0.52	-
7	THF	80		61.5	65.78	0.52	40
8	DCE	80		61.5	65.78	0.52	69

^[a] Conversion determined by analysis of ^1H NMR spectra by comparison of integration of Cp peaks at 5.49 (s, 5H, C_5H_5 , product) and 5.54 (s, 5H, C_5H_5 , starting material).

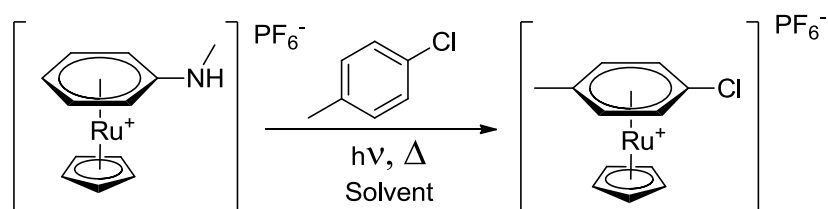
Synthesis of $[\text{RuCp}(\eta^6\text{-N-methylaniline})]\text{PF}_6$ 3.28:



$[\text{RuCp}(\text{MeCN})_3]\text{PF}_6$ (200 mg, 0.46 mmol) and *N*-methylaniline (149.5 μL , 147.9 mg, 1.38 mmol) were placed in degassed 1,2-dichloroethane (20 mL) (degassed by three freeze-thaw cycles) in a Schlenk tube under an N_2 atmosphere, the reaction was then heated to 80 °C for 24 hours. The reaction was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction was left under high

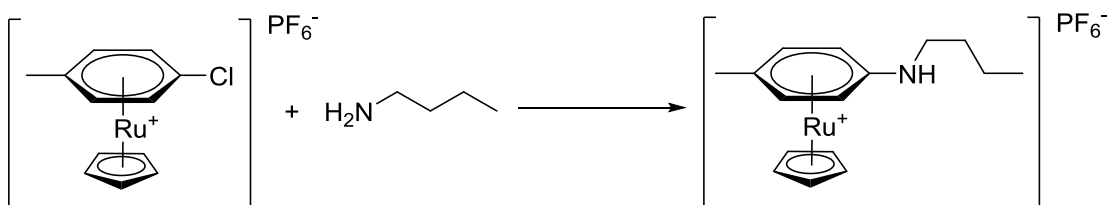
vacuum for 30 min to remove excess *N*-methylaniline. The product was recrystallised by dissolving the reaction mixture in the minimum amount of DCM followed by the slow addition of diethyl ether, which afforded a brown precipitate which was collected to give the product as a brown powder (133 mg, 69% yield). ^1H NMR (250 MHz, $(\text{CD}_3)_2\text{CO}$) δ 6.09-6.05 (m, 2H, C_6H_5), 5.95-5.92 (m, 3H, C_6H_5), 5.73 (s, 1H, NH), 5.36 (s, 5H, C_5H_5), 2.82 (d, $J=5.1$ Hz, 3H, NHCH_3); ^{13}C NMR 125 MHz, $(\text{CD}_3)_2\text{CO}$) δ 87.1, 84.5, 81.4, 81.3, 79.4, 30.2; ^{19}F NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ -72.39 (d, $J=700$ Hz, PF_6). HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{NRu}^+$: 274.0164; Found: 274.0178.

Arene exchange reactions 3.28/3.24:



$[\text{RuCp}(\eta^6\text{-}N\text{-Methylaniline})]\text{PF}_6$ (10 mg, 0.024 mmol) and 4-chlorotoluene (56.7 μL , 60.7 mg, 0.48 mmol) were placed in degassed acetonitrile:DCE or acetonitrile:THF (0.5:0.5 mL) (degassed by bubbling N_2 through for 30 min) in a Schlenk tube under an N_2 atmosphere, the reaction was then heat at 80 $^\circ\text{C}$ and irradiated with a 400 W mercury medium pressure lamp for 16 hours. The reaction was allowed to cool and the solvent removed *in vacuo*. No conversion determined by analysis of ^1H NMR spectra.

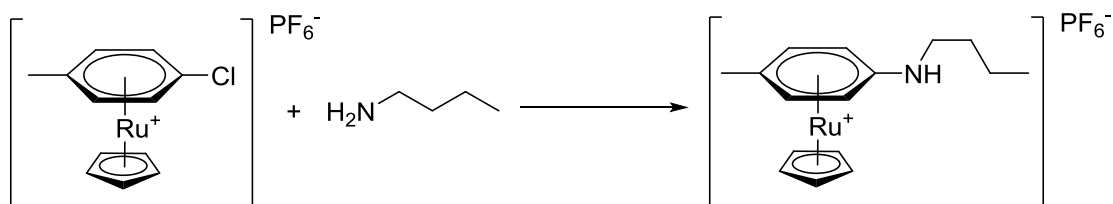
Synthesis of $[\text{RuCp}(\eta^6\text{-}N\text{-butylaniline})]\text{PF}_6$ 3.25:



$[\text{RuCp}(\eta^6\text{-}4\text{-Chlorotoluenyl})]\text{PF}_6$ (10 mg, 0.023 mmol) and butylamine (22.7 μL , 16.8 mg, 0.23 mmol) in THF (0.5 mL) were heated to 80 $^\circ\text{C}$ and irradiated with a 400 W

mercury medium pressure lamp for 16 hours. The reaction was then allowed to cool to room temperature and the solvent removed *in vacuo* 89% conversion determined by analysis of ^1H NMR spectra by comparison of integration of Cp peak in starting material and product. ^1H NMR (250 MHz, $(\text{CD}_3)_2\text{CO}$) δ 6.07-6.05 (d, J = 5.9 Hz, 2H, C_6H_4), 5.96 (d, J = 5.9 Hz, 2H, C_6H_4), 5.30 (s, 5H, C_5H_5), 3.40 (m, 2H, NCH_2CH_2), 2.27 (s, 3H, PhCH_3), 1.70-1.60 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.51-1.34 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.99-0.89 (m, 3H, CH_2CH_3); HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{Ru}^+$: 330.0796; Found: 330.0803.

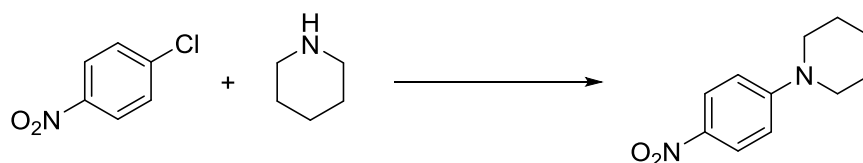
Synthesis of $[\text{RuCp}(\eta^6\text{-N-butylaniline})]\text{PF}_6$ 3.25:



$[\text{RuCp}(\eta^6\text{-4-Chlorotoluene})]\text{PF}_6$ (10 mg, 0.023 mmol) and butylamine (22.7 μL , 16.8 mg, 0.23 mmol) in THF (0.5 mL) were irradiated with a 400 W mercury medium pressure lamp for 16 hours. The solvent removed *in vacuo* 79% conversion determined by analysis of ^1H NMR spectra by comparison of integration of Cp peak in starting material and product. ^1H NMR (250 MHz, $(\text{CD}_3)_2\text{CO}$) δ 6.05 (d, J = 6.4 Hz, 2H, C_6H_4), 5.95 (d, J = 6.4 Hz, 2H, C_6H_4), 5.29 (s, 5H, C_5H_5), 3.39 (t, J = 6.8 Hz 2H, NCH_2CH_2), 2.28 (s, 3H, PhCH_3), 1.68-1.59 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.47-1.36 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.97-0.89 (m, 3H, CH_2CH_3); HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{Ru}^+$: 330.0796; Found: 330.0810.

6.3 Experimental procedure: Chapter 4

(Thio)urea screen

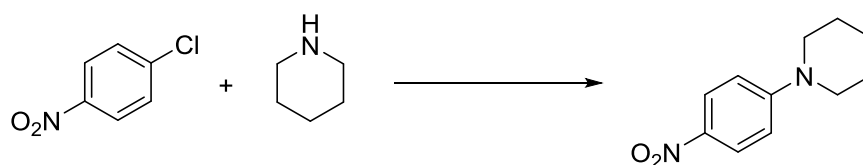


1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (148 μ L, 127.7 mg, 1.5 mmol) and catalyst (X mg, 0.1 mmol) were added to a carousel tube followed by toluene (1 mL), the reaction mixture was stirred at 80 °C for 24 hours. The reaction mixture was allowed to cool to room temperature, filtered and the solvent removed *in vacuo*.

Urea	Catalyst (mg)	Conversion (%) ^[a]
Background	0	8
1,3-Diisopropylthiourea	16.0	12
<i>N,N'</i> -Diphenylthiourea	22.8	11
<i>N,N'</i> -Dimethylurea	8.8	20
1,3-Diphenylurea	21.2	18
Urea	6	9

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Increasing equivalents of urea

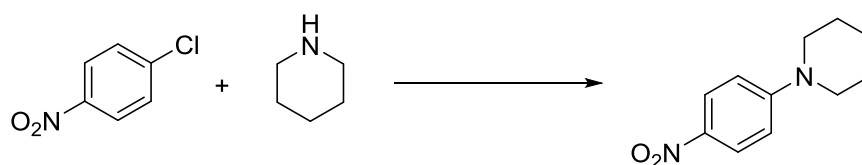


1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (148 μ L, 127.7 mg, 1.5 mmol) and catalyst (X mg, Y mmol) were added to a carousel tube followed by toluene (1 mL), the reaction mixture was stirred at 80 °C for 24 hours. The reaction mixture was allowed to cool to room temperature, filtered and the solvent removed *in vacuo*.

Urea	Catalyst (mmol)	Catalyst (mg)	Conversion (%) ^[a]
Background	0	0	8
1,3-Diphenylurea	0.05	10.6	16
	0.1	21.2	20
	0.2	42.4	22
	0.5	106.1	19
<i>N,N'</i> -Dimethylurea	0.05	4.4	16
	0.1	8.8	19
	0.2	17.6	31
	0.5	44.1	42

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Solvent screen

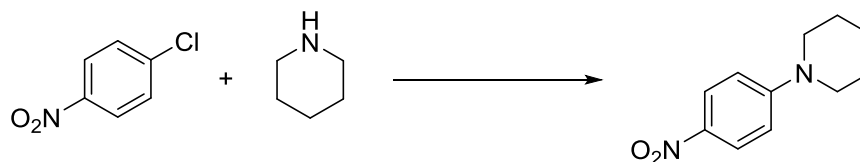


1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (148 μ L, 127.7 mg, 1.5 mmol) and *N,N'*-diphenylurea (21.2 mg, 0.1 mmol) or *N,N'*-dimethylurea (8.8 mg, 0.1 mmol) were added to a carousel tube followed by solvent (1 mL), the reaction mixture was stirred at 80 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

Solvent	1,3-Diphenylurea Conversion ^[a] (%)	<i>N,N'</i> -Dimethylurea Conversion ^[a] (%)	Background Conversion ^[a] (%)
Toluene	16	23	10
DCE	1	2	2
Hexane	22	35	13
THF	42	37	34
Ethanol	40	36	34
Cyclohexane	11	32	11
IPA	33	34	24
Ethyl acetate	30	36	23
Water	27	14	10
Octane	12	34	9
2-Pentanol	36	33	31

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Comparison of octane, cyclohexane and THF

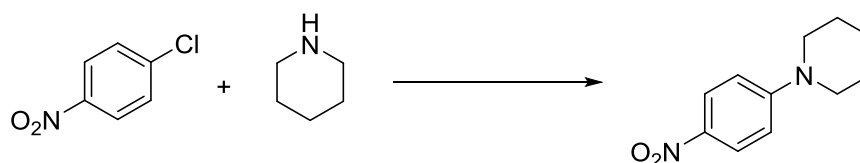


1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (148 μ L, 127.7 mg, 1.5 mmol) and *N,N'*-dimethylurea (X mg, Y mmol) were added to a carousel tube followed by solvent (1 mL), the reaction mixture was stirred at 80 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

Catalyst (mmol)	Catalyst (mg)	Octane Conversion ^[a] (%)	Cyclohexane Conversion ^[a] (%)	THF Conversion ^[a] (%)
0	0	5	10	33
0.1	8.8	38	26	44
0.5	44.1	63	56	52
1.0	88.1	67	64	61
1.5	132.2	68	73	61
2.0	176.2	71	69	62

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

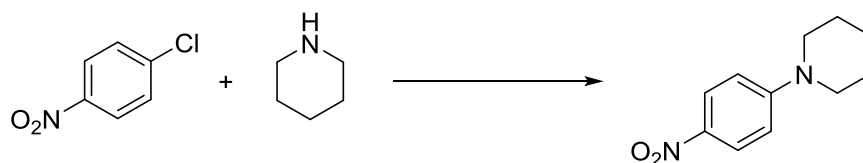
Temperature screen



1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (148 μ L, 127.7 mg, 1.5 mmol) and *N,N'*-dimethylurea (X mg, Y mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at T °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

<i>N,N'</i> -dimethylurea (mmol)	<i>N,N'</i> -dimethylurea (mg)	90 °C Conversion ^[a] (%)	100 °C Conversion ^[a] (%)	110 °C Conversion ^[a] (%)
0	0	17	20	21
0.1	8.8	45	56	52
0.2	17.6	55	59	56
0.4	35.2	64	65	66
0.6	52.9	67	65	68
0.8	70.5	67	70	69
1	88.1	69	72	68

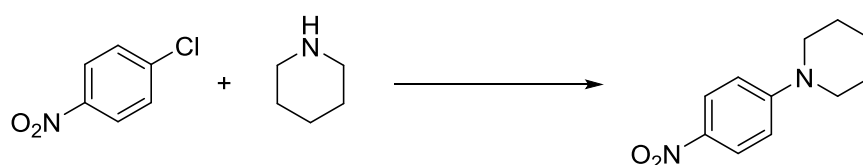
^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Exploration of increasing equivalents of piperidine

1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (247 μ L, 212.8 mg, 2.5 mmol) and *N,N'*-dimethylurea (X mg, Y mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at T °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

<i>N,N'</i> - dimethylurea (mmol)	<i>N,N'</i> - dimethylurea (mg)	80 °C Conv. ^{[a][b]} (%)	90 °C Conv. ^{[a][b]} (%)	100 °C Conv. ^{[a][b]} (%)	90 °C Conv. ^{[a][c]} (%)	90 °C Conv. ^{[a][d]} (%)
0	0	17	24	34	8	12
0.4	35.2	84	83	89	57	59
0.6	52.9	88	92	94	63	69

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene). ^[b] Piperidine (2.5 mmol) added. ^[c] Triethylamine (1.5 mmol) and piperidine (1.5 mmol) added. ^[d] Potassium carbonate (1.5 mmol) and piperidine (1.5 mmol) added.

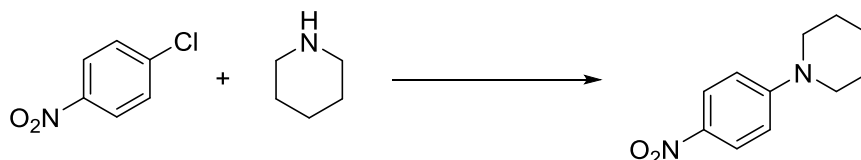
Exploring the use of molecular sieves

1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (148 μ L, 127.7 mg, 1.5 mmol), *N,N'*-dimethylurea (X mg, Y mmol) and 4 Å molecular sieves (MS) (100 mg) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 90 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

<i>N,N'</i> -dimethylurea (mmol)	<i>N,N'</i> -dimethylurea (mg)	Beaded MS Conversion ^[a] (%)	Powdered MS Conversion ^[a] (%)
0	0	20	10
0.4	35.2	62	68
0.6	52.9	66	72
0.8	70.5	66	74
1	88.1	72	74

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

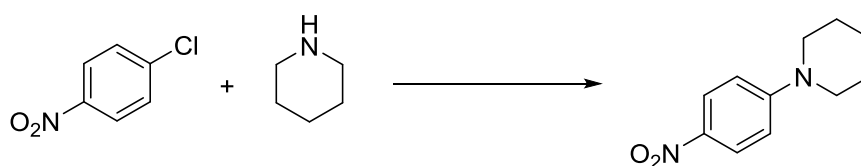
2.0 equivalents of piperidine



1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (198 μ L, 170.2 mg, 2.0 mmol) and *N,N'*-dimethylurea (X mg, Y mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 90 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

<i>N,N'</i> -dimethylurea (mmol)	<i>N,N'</i> -dimethylurea (mg)	Conversion ^[a] (%)
0	17	15
0.2	17.6	60
0.4	35.2	78
0.6	52.9	78
0.8	70.5	85
1	88.1	83

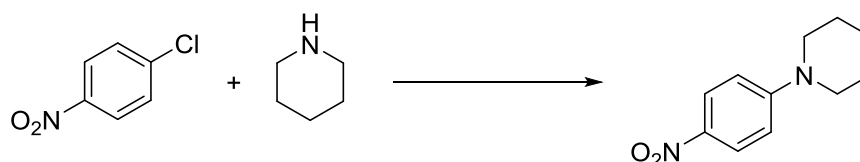
^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

2.5 equivalents of piperidine

1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (247 μ L, 212.8 mg, 2.5 mmol) and *N,N'*-dimethylurea (X mg, Y mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 90 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

<i>N,N'</i> -dimethylurea (mmol)	<i>N,N'</i> -dimethylurea (mg)	Conversion ^[a] (%)
0	17	24
0.2	17.6	77
0.4	35.2	91
0.6	52.9	91
0.8	70.5	94
1	88.1	93

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

3.0 equivalents of piperidine

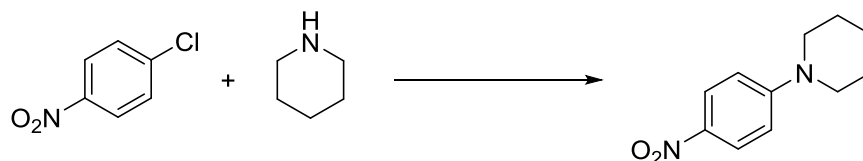
1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (296 μ L, 255.4 mg, 3.0 mmol) and *N,N'*-dimethylurea (X mg, Y mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 90 °C for 24 hours.

The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

<i>N,N'</i> - dimethylurea (mmol)	<i>N,N'</i> - dimethylurea (mg)	1 st repeat Conversion ^[a] (%)	2 nd repeat Conversion ^[a] (%)
0	0	28	28
0.2	17.6	80	85
0.4	35.2	95	97
0.6	52.9	96	99
0.8	70.5	100	99.5
1	88.1	95	99.5

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Time monitored reaction

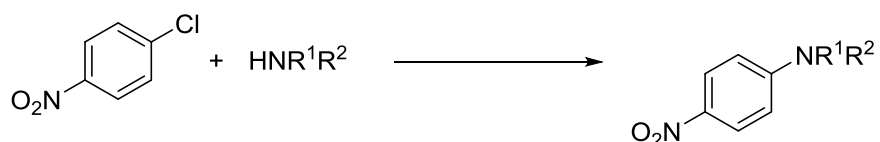


1-Chloro-4-nitrobenzene (472.78 mg, 3 mmol), piperidine (889 μ L, 766.14 mg, 9.0 mmol) and *N,N'*-dimethylurea (105.7 mg, 1.2 mmol) were added to a carousel tube followed by octane (3 mL), the reaction mixture was stirred at 90 °C for 24 hours. Samples (0.2 mL) were taken every hour (for 1-8 and 16-24 hours), the sample was allowed to cool to room temperature and the solvent removed *in vacuo*. Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Time (h)	Conversion ^[a] (%)
1	11
2	23
3	36
4	46
5	52
6	59
7	68
8	71
16	91
17	93
18	93
19	93
20	93
21	94
22	98
23	95
24	99

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 6.76 (d, 2H, CH, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

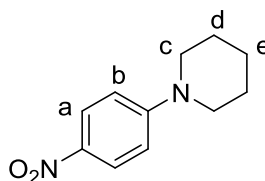
General procedure 4.1



1-Chloro-4-nitrobenzene (1 equiv), amine (3 equiv) and *N,N'*-dimethylurea (0.5 equiv) were added to a carousel tube followed by octane (1 M), the reaction mixture was stirred at 90 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction mixture was

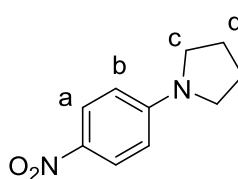
then dissolved in DCM (20 mL) and washed with water (3 x 20 mL). The aqueous layer were combined and extracted with DCM (3 x 10 mL). The organic fractions were combined, dried over magnesium sulfate, followed by filtration and the solvent removed *in vacuo*.

Synthesis of 1-(4-nitrophenyl)piperidine **4.2**¹⁵⁷



Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), piperidine (889 μ L, 766.1 mg, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (30 % ethyl acetate/ pentane) gave the desired product as a yellow solid (550 mg, 2.66 mmol, 89% yield). Mp 105-106 $^{\circ}$ C [lit. mp 104-105 $^{\circ}$ C]. ^1H NMR (500 MHz, CDCl_3) δ 8.08 (d, $J=9.8$ Hz, 2H, a), 6.77 (d, $J=9.8$ Hz, 2H, b), 3.43 (br s, 4H, c), 1.68 (br s, 6H, d + e); ^{13}C NMR (125 MHz, CDCl_3) δ 154.8, 137.2, 126.0, 112.2, 48.3, 25.2, 24.2. HRMS calcd for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_2^+$: 207.1136; Found: 207.1147.

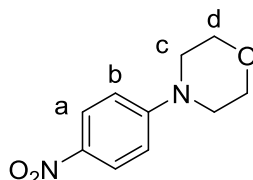
Synthesis of 1-(4-nitrophenyl)pyrrolidine **4.8**¹⁵⁷



Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), pyrrolidine (751 μ L, 640.1 mg, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (20% ethyl acetate/pentane) gave the desired product as a yellow solid (547 mg, 2.84 mmol, 95% yield). Mp 166-168 $^{\circ}$ C [lit. mp 166-168 $^{\circ}$ C]. ^1H NMR (500 MHz, CDCl_3) δ 8.08 (d, $J=9.3$ Hz 2H, a), 6.44 (d, $J=9.3$ Hz, 2H, b), 3.39 (t, $J=6.6$ Hz, 4H, c),

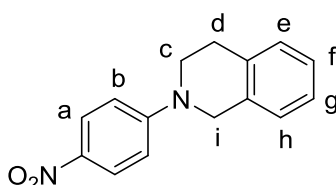
2.07 (t, $J=6.6$ Hz, 4H, d); ^{13}C NMR (125 MHz, CDCl_3) δ 151.8, 136.3, 126.2, 110.3, 47.8, 25.3. HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_2^+$: 193.0977; Found: 193.0981.

Synthesis of 4-(4-nitrophenyl)morpholine 4.9¹⁵⁷

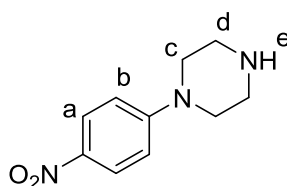


Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), morpholine (787 μL , 784.1 mg, 9.0 mmol) and N,N' -dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (20-40% ethyl acetate/pentane) gave the desired product as an orange solid (546 mg, 2.61 mmol, 87% yield). Mp 151-153 $^{\circ}\text{C}$ [lit. mp 149-151 $^{\circ}\text{C}$]. ^1H NMR (500 MHz, CDCl_3) δ 8.17 (d, $J=9.3$ Hz 2H, a), 6.84 (d, $J=9.3$ Hz, 2H, b), 3.87 (t, $J=4.9$ Hz, 4H, d), 3.38 (t, $J=4.9$ Hz, 4H, c); ^{13}C NMR (125 MHz, CDCl_3) δ 154.9, 138.8, 125.8, 112.5, 66.3, 47.0. HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_3^+$: 209.0926; Found: 209.0918.

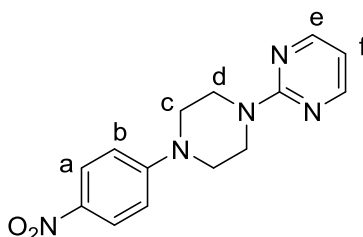
Synthesis of 2-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline 4.10¹⁵⁸



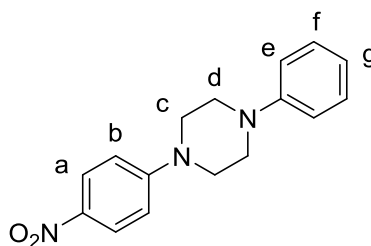
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), 1,2,3,4-tetrahydroisoquinoline (1.13 mL, 1.20 g, 9.0 mmol) and N,N' -dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (100% DCM) gave the desired product as an orange solid (584 mg, 2.31 mmol, 77% yield). Mp 154-156 $^{\circ}\text{C}$ [lit. mp 152-154 $^{\circ}\text{C}$]. ^1H NMR (500 MHz, CDCl_3) δ 8.18 (d, $J=9.3$ Hz 2H, a), 7.28-7.20 (m, 4H, e - h), 6.84 (d, $J=9.3$ Hz, 2H, b), 4.59 (s, 2H, i) 3.71 (t, $J=5.9$ Hz, 2H, c), 3.04 (t, $J=5.9$ Hz, 2H, d); ^{13}C NMR (125 MHz, CDCl_3) δ 153.7, 137.4, 134.8, 133.0, 128.0, 127.0, 126.6, 126.4, 126.0, 111.0, 48.7, 44.6, 28.8. HRMS calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_2^+$: 255.1134; Found: 255.1117.

Synthesis of 1-(4-nitrophenyl)piperazine 4.11¹⁵⁹

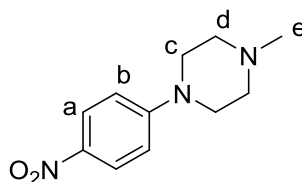
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), piperazine (775.3 mg, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (0-8% methanol/DCM) gave the desired product as a brown solid (559 mg, 2.70 mmol, 90% yield). Mp 132-134 °C [lit. mp 129-130 °C]. ¹H NMR (500 MHz, CDCl₃) δ 8.13 (d, J=9.3 Hz 2H, a), 6.82 (d, J=9.3 Hz, 2H, b), 3.39 (t, J=5.4 Hz, 4H, c), 3.03 (t, J=4.9 Hz, 4H, d), 1.77 (s, 1H, e); ¹³C NMR (125 MHz, CDCl₃) δ 155.1, 138.1, 125.8, 112.4, 47.9, 45.6. HRMS calcd for C₁₀H₁₄N₃O₂⁺: 208.1008; Found: 208.1099.

Synthesis of 2-(4-(4-nitrophenyl)piperazin-1-yl)pyrimidine 4.12¹⁶⁰

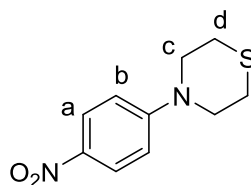
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.78 mg, 3 mmol), 1-(2-pyrimidyl)piperazine (1.40 mL, 1.48 g, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (0-2% methanol/DCM) gave the desired product as an orange solid (430 mg, 1.50 mmol, 50% yield). Mp 240-242 °C [lit. mp 245-247 °C]. ¹H NMR (500 MHz, CDCl₃) δ 8.36 (d, J=4.4 Hz 2H, e), 8.16 (d, J=9.8 Hz 2H, a), 6.86 (d, J=9.8 Hz, 2H, b), 6.58 (t, J=4.9 Hz 1H, f), 4.02 (t, J=5.4 Hz, 4H, c), 3.55 (t, J=5.4 Hz, 4H, d); ¹³C NMR (125 MHz, CDCl₃) δ 157.8, 154.7, 138.6, 126.0, 112.6, 110.5, 110.0, 46.7, 43.0. HRMS calcd for C₁₄H₁₆N₅O₂⁺: 286.1304; Found: 286.1291.

Synthesis of 1-(4-nitrophenyl)-4-phenylpiperazine 4.13¹⁶⁰

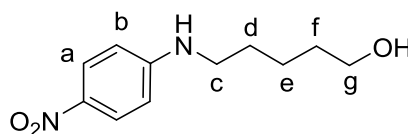
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), 1-phenylpiperazine (1.37 mL, 1.46 g, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (0-5% methanol/DCM) gave the desired product as a brown solid (404 mg, 1.44 mmol, 48% yield). Mp 198-200 °C [lit. mp 175-177 °C]. ¹H NMR (500 MHz, CDCl₃) δ 8.17 (d, J=9.3 Hz 2H, a), 7.33 (m, 2H, f), 6.99 (d, J=7.8 Hz 2H, e), 6.94 (t, J=7.3 Hz 1H, g), 6.89 (d, J=9.3 Hz, 2H, b), 3.61 (t, J=4.9 Hz, 4H, c), 3.38 (t, J=4.9 Hz, 4H, d); ¹³C NMR (125 MHz, CDCl₃) δ 154.7, 138.7, 129.3, 126.0, 120.5, 116.3, 112.8, 99.7, 48.9, 47.1. HRMS calcd for C₁₆H₁₈N₃O₂⁺: 284.1399; Found: 284.1394.

Synthesis of 1-methyl-4-(4-nitrophenyl)piperazine 4.14¹⁶⁰

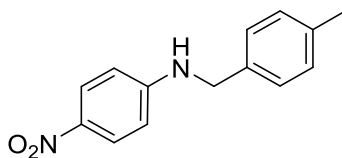
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), 1-methylpiperazine (998 µL, 901.4 mg, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (0-5% methanol/DCM) gave the desired product as an orange solid (487 mg, 2.19 mmol, 73% yield). Mp 108-110 °C [lit. mp 108-110 °C]. ¹H NMR (500 MHz, CDCl₃) δ 8.13 (d, J=9.3 Hz 2H, a), 6.83 (d, J=9.3 Hz, 2H, b), 3.54 (t, J=5.4 Hz, 4H, c), 2.57 (t, J=5.4 Hz, 4H, d), 2.37 (s, 3H, e); ¹³C NMR (125 MHz, CDCl₃) δ 154.8, 138.2, 125.9, 112.6, 54.5, 46.9, 46.0. HRMS calcd for C₁₁H₁₆N₃O₂⁺: 222.1243; Found: 222.1244.

Synthesis of 4-(4-nitrophenyl)thiomorpholine 4.15¹⁶¹

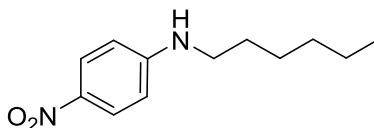
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), thiomorpholine (903 μ L, 928.7 mg, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (100% DCM) gave the desired product as a yellow solid (320 mg, 1.44 mmol, 48% yield). Mp 143-145 $^{\circ}$ C [lit. mp 140-143 $^{\circ}$ C]. ^1H NMR (500 MHz, CDCl_3) δ 8.14 (d, $J=9.3$ Hz 2H, a), 6.78 (d, $J=9.3$ Hz, 2H, b), 3.87 (t, $J=5.4$ Hz, 4H, c), 2.72 (t, $J=5.4$ Hz, 4H, d); ^{13}C NMR (125 MHz, CDCl_3) δ 153.2, 137.4, 125.9, 112.4, 49.9, 25.5. HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_2\text{S}^+$: 225.0698; Found: 225.0680.

Synthesis of 5-((4-nitrophenyl)amino)pentan-1-ol 4.16¹⁶²

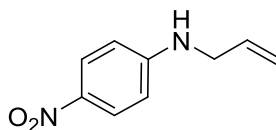
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), 5-amino-1-pentanol (1.12 mL, 911 mg, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) were combined. Purification by column chromatography (0-10% methanol/DCM) gave a yellow solid (357 mg, 1.47 mmol, 49% yield). Mp 78-80 $^{\circ}$ C. ^1H NMR (500 MHz, CDCl_3) δ 8.09 (d, $J=9.3$ Hz 2H, a), 6.52 (d, $J=9.3$ Hz, 2H, b), 3.70 (t, $J=6.4$ Hz, 2H, g), 3.24 (t, $J=7.1$ Hz, 2H, c), 1.74-1.68 (m, 2H, f), 1.67-1.62 (m, 2H, d), 1.55-1.49 (m, 2H, e); ^{13}C NMR (125 MHz, CDCl_3) δ 153.6, 137.3, 126.4, 110.8, 62.4, 43.2, 32.1, 28.4, 23.2. HRMS calcd for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_3^+$: 225.1239; Found: 225.1222.

Synthesis of *N*-(4-methylbenzyl)-4-nitroaniline 4.19

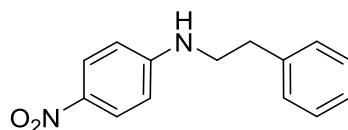
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.78 mg, 3 mmol), 4-methyl-1-benzylamine (1.15 mL, 1.09 g, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) gave 10% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 6.54 (d, 2H, CH₃, product) and 7.50 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Synthesis of *N*-hexyl-4-nitroaniline 4.20¹⁶³

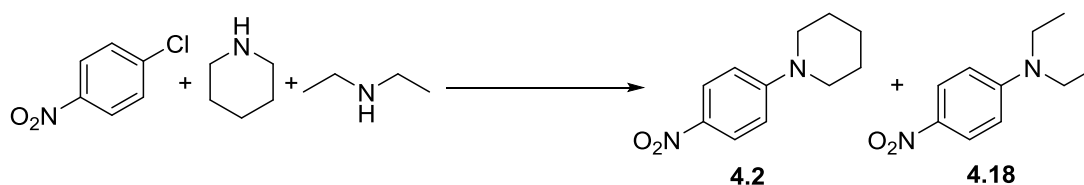
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), hexylamine (1.12 mL, 910.7 mg, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) gave 12% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 6.51 (d, 2H, CH, product) and 7.52 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Synthesis of *N*-allyl-4-nitroaniline 4.21¹⁶³

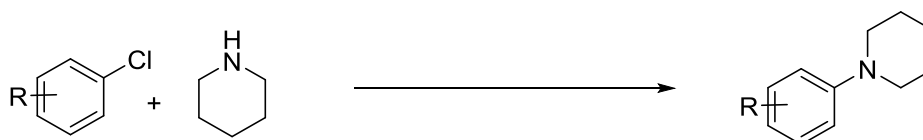
Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), allylamine (675 μL , 513.8 mg, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) gave 5% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 6.55 (d, 2H, CH, product) and 7.51 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Synthesis of 4-nitro-*N*-phenethylaniline 4.22

Following general procedure 4.1, 1-chloro-4-nitrobenzene (472.8 mg, 3 mmol), phenethylamine (1.13 mL, 1.09 g, 9.0 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) in octane (3 mL) gave 14% conversion to the desired product determined, by analysis of ^1H NMR spectra by comparison of peaks at 6.52 (d, 2H, CH, product) and 7.51 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Competition experiment¹⁵⁷

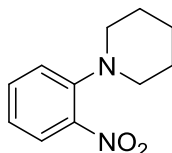
1-Chloro-4-nitrobenzene (157.5 mg, 1 mmol), piperidine (296 μL , 255.4 mg, 3.0 mmol), diethylamine (311 μL , 219.5 mg, 3.0 mmol) and *N,N'*-dimethylurea (44.06 mg, 0.5 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 90 $^{\circ}\text{C}$ for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Interpretation of ^1H NMR spectra showed 100% conversion to **4.2** and no conversion to **4.18**.

General procedure 4.2

Arene (1 equiv), piperidine (1.5 equiv) and *N,N'*-dimethylurea (1 equiv) or 1,3-diphenylurea (1 equiv) were added to a carousel tube followed by octane (1 mL),

the reaction mixture was stirred at 90 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

Synthesis of 1-(2-nitrophenyl)piperidine 4.26¹⁶⁴



Following general procedure 4.2, 1-chloro-2-nitrobenzene (157.7 mg, 1 mmol), piperidine (148 μ L, 127.7 mg, 1.5 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) or 1,3-diphenylurea (212.25 mg, 1.0 mmol) in octane (1 mL) were combined. Conversions determined by analysis of ^1H NMR spectra by comparison of peaks at 7.81 (dd, 1H, CH, product) and 7.66 (dd, 1H, CH, 1-chloro-2-nitrobenzene).

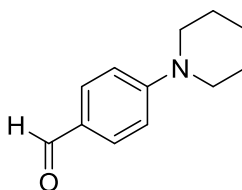
Conversions:

Background: 66%

N,N'-Dimethylurea: 65%

1,3-Diphenylurea: 59%

Synthesis of 4-(piperidin-1-yl)benzaldehyde 4.29¹⁶⁵



Following general procedure 4.2, 4-chlorobenzaldehyde (140.7 mg, 1 mmol), piperidine (148 μ L, 127.7 mg, 1.5 mmol) and *N,N'*-dimethylurea (132.2 mg, 1.5 mmol) or 1,3-diphenylurea (212.25 mg, 1.0 mmol) in octane (1 mL) were combined. Conversions determined by analysis of ^1H NMR spectra by comparison of peaks at 7.13 (d, 2H, CH, product) and 7.48 (d, 2H, CH, 1-chloro-4-nitrobenzene).

Conversions:

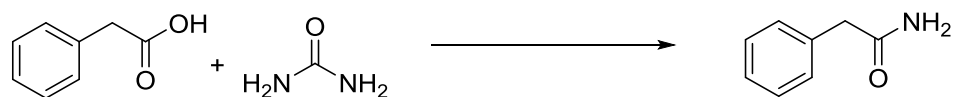
Background: 69%

N,N'-Dimethylurea: 67%

1,3-Diphenylurea: 62%

6.4 Experimental procedure: Chapter 5

Catalyst screen with 1 equivalent of urea

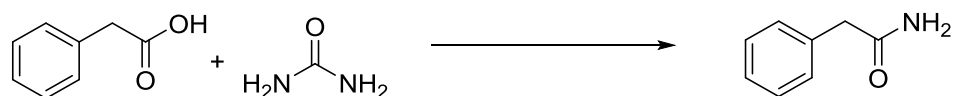


Phenylacetic acid (136.2 mg, 1 mmol), urea (60.1 mg, 1.0 mmol) and catalyst (X mg, Y mmol) were added to a carousel tube followed by octane (1 mL), and the reaction mixture was stirred at 110 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

Catalyst	Catalyst (mmol)	Catalyst (mg)	Conversion (%) ^[a]
Imidazole	0.1	6.8	59
Imidazole	0.2	13.6	78
DMAP	0.1	12.2	58
DMAP	0.2	24.4	71
Background	0	0	24

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.38 (s, 2H, CH₂, product) and 3.48 (s, 2H, CH₂, acid).

Catalyst screen with 1.5 equivalent of urea

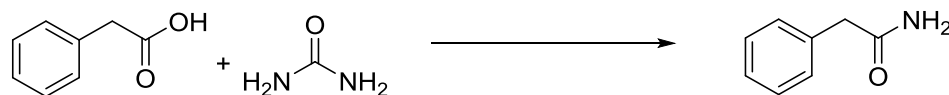


Phenylacetic acid (136.2 mg, 1 mmol), urea (90.1 mg, 1.5 mmol) and catalyst (X mg, Y mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 110 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

Catalyst	Catalyst (mmol)	Catalyst (mg)	Conversion (%) ^[a]
Imidazole	0.1	6.8	71
Imidazole	0.2	13.6	86
Imidazole	0.3	20.4	85
DMAP	0.1	12.2	74
DMAP	0.2	24.4	84
1-Methylimidazole	0.2	16.4	66
2-Methylimidazole	0.2	16.4	37
Background	0	0	24

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.38 (s, 2H, CH₂, product) and 3.48 (s, 2H, CH₂, acid).

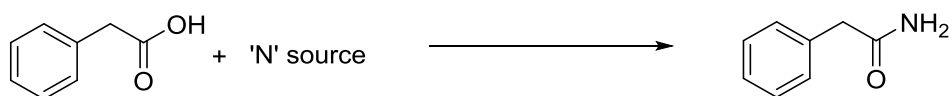
Catalyst screen with 2 equivalent of urea



Phenylacetic acid (136.2 mg, 1 mmol), urea (120.1 mg, 2.0 mmol) and catalyst (X mg, Y mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 110 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

Catalyst	Catalyst (mmol)	Catalyst (mg)	Conversion (%) ^[a]
Imidazole	0.1	6.8	72
Imidazole	0.2	13.6	84
DMAP	0.1	12.2	71
DMAP	0.2	24.4	84
Background	0	0	25

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.38 (s, 2H, CH₂, product) and 3.48 (s, 2H, CH₂, acid).

'N' Source screen

Phenylacetic acid (136.2 mg, 1 mmol), N source (X mg, 1.5 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 110 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

'N' source	mg	Conversion (%) ^[a]
Urea	90.1	86
Ammonium chloride	80.2	0
Ammonium formate	94.6	19
Ammonium acetate	115.6	20
Ammonium iodide	217.4	0
Ammonium carbamate	144.1	13
Formamide	67.6	32

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.38 (s, 2H, CH₂, product) and 3.48 (s, 2H, CH₂, acid).

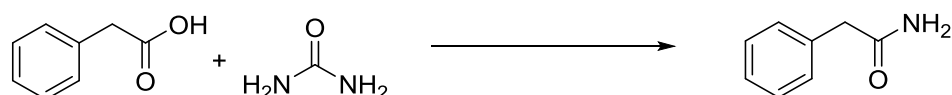
Solvent Screen

Phenylacetic acid (136.2 mg, 1 mmol), urea (90.1 mg, 1.5 mmol) or formamide (59.6 μL, 67.6 mg, 1.5 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by solvent (1 mL), the reaction mixture was stirred at 80 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

'N' source	Urea Conversion (%) ^[a]	Formamide Conversion (%) ^[a]
Water	0	0
1-Propanol	0	0
Ethanol	0	0
Ethyl acetate	0	0
Octane	10	6
Cyclohexane	8	8
Toluene	5	8
2-MethylTHF	0	0

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.38 (s, 2H, CH₂, product) and 3.48 (s, 2H, CH₂, acid).

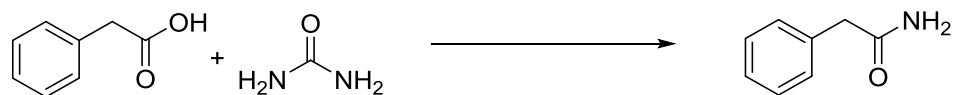
Temperature screen



Phenylacetic acid (136.2 mg, 1 mmol), urea (90.1 mg, 1.5 mmol) and imidazole (13.6 mg, 0.2 mmol) or DMAP (24.4 mg, 0.2 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at T °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

Temperature (°C)	Imidazole Conversion (%) ^[a]	DMAP Conversion (%) ^[a]	Background Conversion (%) ^[a]
80	10	8	3
90	27	24	7
100	50	48	15
110	86	84	24
120	96	90	33
126	96	89	37

^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.38 (s, 2H, CH₂, product) and 3.48 (s, 2H, CH₂, acid).

Concentration screen

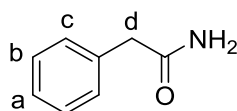
Phenylacetic acid (136.2 mg, 1 mmol), urea (90.1 mg, 1.5 mmol) and imidazole (13.6 mg, 0.2 mmol) or DMAP (24.4 mg, 0.2 mmol) were added to a carousel tube followed by octane (X mL), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

Octane (mL)	Imidazole Conversion (%) ^[a]	DMAP Conversion (%) ^[a]	Background Conversion (%) ^[a]
2 mL	87	88	28
1 mL	98	91	33
0.5 mL	95	90	34

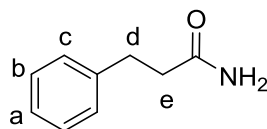
^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.38 (s, 2H, CH₂, product) and 3.48 (s, 2H, CH₂, acid).

General procedure 5.1

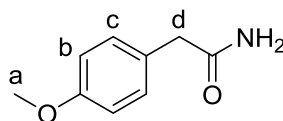
Carboxylic acid (1 equiv), urea (1.5 equiv) and imidazole (0.2 equiv) were added to a carousel tube followed by octane (1 M), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction mixture was then dissolved in ethyl acetate (15 mL) and extracted with 1 M aqueous sodium bicarbonate (3 x 20 mL). The aqueous layer were combined and extracted with ethyl acetate (5 x 20 mL). The organic fractions were combined, dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the desired product.

Synthesis of 2-phenylacetamide 5.6¹⁴⁶

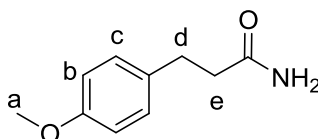
Following general procedure 5.1, phenylacetic acid (408.5 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as an off white solid (405.5 mg, 2.73 mmol, 91% yield). Mp 157-159 °C [lit. mp 155-158 °C]. ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.36 (m, 2H, c), 7.32-7.28 (m, 3H, a+b), 5.54 (br s, 1H, NH), 5.39 (br s, 1H, NH) 3.60 (s, 2H, d); ¹³C NMR (125 MHz, CDCl₃) δ 173.6, 134.8, 129.4, 129.0, 127.4, 43.3. HRMS calcd for C₈H₁₀NO⁺: 136.0762; Found: 136.0781.

Synthesis of 3-phenylpropanamide 5.7¹⁶⁶

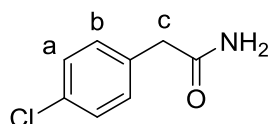
Following general procedure 5.1, hydrocinnamic acid (450.5 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as a white solid (432 mg, 2.91 mmol, 97% yield). Mp 101-103 °C [lit. mp 102-104 °C]. ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.29 (m, 2H, c), 7.23-7.21 (m, 3H, a+b), 5.43 (br s, 1H, NH), 5.35 (br s, 1H, NH), 2.99 (t, J=7.8 Hz, 2H, d), 2.55 (t, J=7.8 Hz, 2H, e); ¹³C NMR (125 MHz, CDCl₃) δ 174.6, 140.6, 128.5, 128.3, 126.3, 37.5, 31.4. HRMS calcd for C₉H₁₂NO⁺: 150.0919; Found: 150.0941.

Synthesis of 2-(4-methoxyphenyl)acetamide 5.8¹⁵³

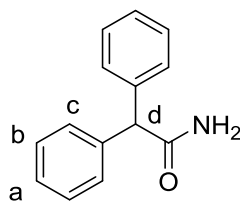
Following general procedure 5.1, 4-methoxyphenylacetic acid (498.5 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) were combined. Purification gave the desired product as a yellow solid (401 mg, 2.43 mmol, 81% yield). Mp 188-190 °C [lit. mp 164-166 °C]. ¹H NMR (500 MHz, CDCl₃) δ 7.2 (d, J=8.3 Hz 2H, c), 6.90 (d, J=8.8 Hz, 2H, b), 5.40 (s, 2H, NH₂), 3.82 (s, 3H, a), 3.54 (s, 2H, d); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 156.9, 128.8, 126.7, 112.5, 53.8, 40.6. HRMS calcd for C₉H₁₂NO₂⁺: 166.0868; Found: 166.0878.

Synthesis of 3-(4-methoxyphenyl)propanamide 5.9¹⁶⁷

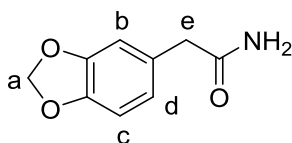
Following general procedure 5.1, 3-(4-methoxyphenyl)propionic acid (540.6 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as a white solid (484 mg, 2.70 mmol, 90% yield). Mp 126-128 °C [lit. mp 123-124 °C]. ¹H NMR (500 MHz, CDCl₃) δ 7.14 (d, J=8.8 Hz 2H, c), 6.84 (d, J=8.8 Hz, 2H, b), 5.57 (br s, 1H, NH), 5.40 (br s, 1H, NH), 3.79 (s, 3H, a) 2.91 (t, J=7.8 Hz, 2H, d), 2.50 (t, J=7.8 Hz, 2H, e); ¹³C NMR (125 MHz, CDCl₃) δ 174.8, 158.0, 132.7, 129.2, 113.9, 55.2, 37.8, 30.5. HRMS calcd for C₁₀H₁₄NO₂⁺: 180.1024; Found: 180.1039.

Synthesis of 2-(4-chlorophenyl)acetamide 5.10¹⁵³

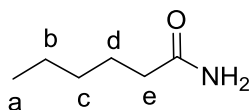
Following general procedure 5.1, 4-chlorophenylacetic acid (511.8 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as a white solid (490 mg, 2.88 mmol, 96% yield). Mp 483-185 °C [lit. mp 179-182 °C]. ¹H NMR (500 MHz, CDCl₃) δ 7.35 (d, J=8.8 & 2.4 Hz, 2H, b), 7.23 (d, J=8.3 & 2.4 Hz, 2H, a), 5.44 (br s, 1H, NH), 5.36 (br s, 1H, NH), 3.57 (s, 2H, c); ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 133.5, 130.8, 129.5, 127.1, 40.6. HRMS calcd for C₈H₈ClNNaO⁺: 192.0192; Found: 192.0188.

Synthesis of 2,2-diphenylacetamide 5.11¹⁶⁸

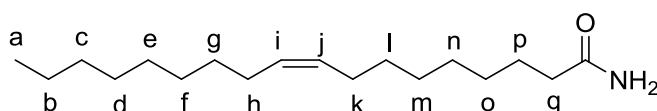
Following general procedure 5.1, diphenylacetic acid (408.5 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as a pale brown solid (428 mg, 2.04 mmol, 68% yield). Mp 166-168 °C [lit. mp 169 °C]. ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.30 (m, 4H, c), 7.27-7.24 (m, 6H, a+b), 6.04 (br s, 1H, NH), 5.57 (br s, 1H, NH), 4.94 (s, 1H, d); ¹³C NMR (125 MHz, CDCl₃) δ 174.9, 139.1, 132.4, 130.0, 128.8, 128.7, 128.4, 128.2, 127.3, 58.7. HRMS calcd for C₁₄H₁₃NNaO⁺: 234.0865; Found: 234.0903.

Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)acetamide 5.12¹⁶⁹

Following general procedure 5.1, 3,4-(methylenedioxy)phenylacetic acid (180.2 mg, 1 mmol), urea (90.1 mg, 1.5 mmol) and imidazole (13.6 mg, 0.2 mmol) were combined in octane (1 mL). Purification gave the desired product as a white solid (162 mg, 0.90 mmol, 90% yield). Mp 174-176 °C [lit. mp 172-173 °C]. ¹H NMR (500 MHz, CDCl₃) δ 6.80 (d, J=7.8 Hz, 1H, c), 6.77 (d, J=1.5 Hz, 1H, b), 6.73 (dd, J=7.8 & 2.0 Hz, 1H, d), 5.97 (s, 2H, a), 5.40 (br s, 2H, NH₂), 3.51 (s, 2H, e); ¹³C NMR (125 MHz, CDCl₃) δ 172.7, 146.9, 145.6, 128.5, 121.5, 108.9, 107.4, 100.1, 41.7. HRMS calcd for C₉H₁₀NO₃⁺: 180.0661; Found: 180.0668.

Synthesis of hexanamide 5.13¹⁵⁰

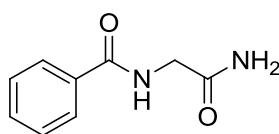
Following general procedure 5.1, hexanoic acid (376 µL, 348.5 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as a white solid (316 mg, 2.67 mmol, 89% yield). Mp 98-100 °C [lit. mp 101-102 °C]. ¹H NMR (500 MHz, CDCl₃) δ 5.59 (br s, NH), 5.45 (br s, NH), 2.22 (t, J=7.3 Hz, 2H, e), 1.68-1.62 (m, 2H, d), 1.36-1.32 (m, 4H, b+c), 0.90 (t, J=7.3 Hz, 3H, a); ¹³C NMR (125 MHz, CDCl₃) δ 176.1, 35.9, 31.3, 25.2, 22.3, 13.8. HRMS calcd for C₆H₁₃NONa⁺: 138.0894; Found: 138.0908.

Synthesis of oleamide 5.14¹⁷⁰

Following general procedure 5.1, oleic acid (952 µL, 847.4 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as a white solid (771 mg, 2.73 mmol, 91%

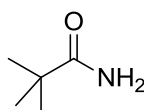
yield). Mp 70-72 °C [lit. mp 71-73 °C]. ^1H NMR (500 MHz, CDCl_3) δ 5.67 (br s, 1H, NH), 5.43 (br s, 1H, NH), 5.36-5.33 (m, 2H, i+j), 2.23 (t, $J=7.3$ Hz, 2H, q), 2.04-2.00 (m, 4H, h+k), 1.67-1.61 (m, 2H, p), 1.32-1.27 (m, 20H, b-g + k-o), 0.89 (t, $J=7.1$ Hz, 2H, a); ^{13}C NMR (125 MHz, CDCl_3) δ 176.2, 130.0, 129.7, 35.9, 31.9, 29.8, 29.7, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 27.2, 27.1, 25.5, 22.7, 14.1. HRMS calcd for $\text{C}_{18}\text{H}_{36}\text{NO}^+$: 282.2797; Found: 282.2772.

Synthesis of *N*-(2-amino-2-oxoethyl)benzamide 5.15¹⁷¹



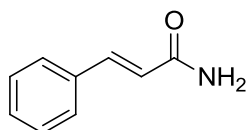
Following general procedure 5.1, hippuric acid (537.5 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 28% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 3.76 (d, 2H, CH_2 , product) and 3.85 (d, 2H, CH_2 , acid).

Synthesis of pivalamide 5.16¹⁷²



Following general procedure 5.1, pivalic acid (345 μL , 306.4 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 26% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 1.07 (s, 9H, $(\text{CH}_3)_3$, product) and 1.10 (s, 9H, $(\text{CH}_3)_3$, acid).

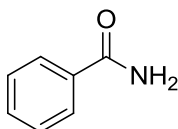
Synthesis of *trans*-cinnamamide 5.17¹⁴⁶



Following general procedure 5.1, *trans*-cinnamic acid (444.5 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 38%

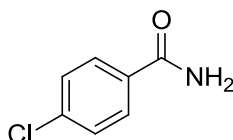
conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 6.51 (s, 1H, CH, product) and 6.50 (s, 1H, CH, acid).

Synthesis of benzamide 5.18¹⁴⁶



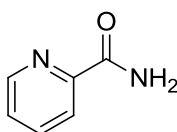
Following general procedure 5.1, benzoic acid (366.4 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 30% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 7.86 (d, 2H, CH₂, product) and 7.89 (d, 2H, CH₂, acid).

Synthesis of 4-chlorobenzamide 5.19¹⁴⁶



Following general procedure 5.1, 4-chlorobenzoic acid (469.7 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 18% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 7.51 (d, 2H, CH₂, product) and 7.46 (d, 2H, CH₂, acid).

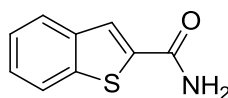
Synthesis of picolinamide 5.20¹⁷³



Following general procedure 5.1, 2-picolinic acid (369.3 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 65%

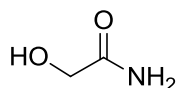
conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 7.40-7.43 (m, 1H, CH₂, product) and 7.57-7.59 (m, 1H, CH₂, acid).

Synthesis of benzo[b]thiophene-2-carboxamide 5.21¹⁷⁴



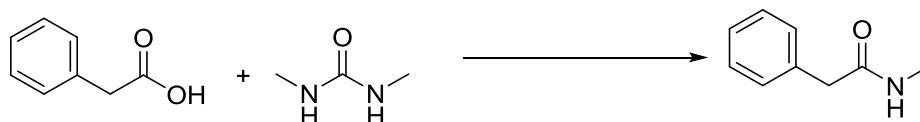
Following general procedure 5.1, thianaphthene-2-carboxylic acid (534.7 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 31% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 7.31-7.37 (m, 2H, CH, product) and 7.39-7.45 (m, 2H, CH, acid).

Synthesis of 2-hydroxyacetamide 5.22¹⁷⁵



Following general procedure 5.1, glycolic acid (228.2 mg, 3 mmol), urea (270.3 mg, 4.5 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 67% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 4.55 (s, 2H, CH₂, product) and 4.25 (s, 2H, CH₂, acid).

Conditions for reactions with substituted ureas



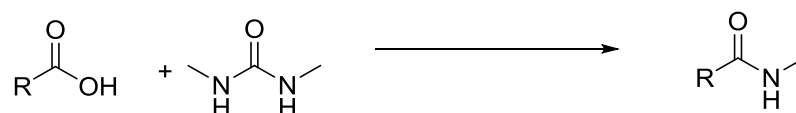
Phenylacetic acid (136.2 mg, 1 mmol), *N,N'*-dimethylurea (X mg, Y mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1

mL), the reaction mixture was stirred at T °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*.

<i>N,N'</i> -dimethylurea (mmol)	<i>N,N'</i> -dimethylurea (mg)	Temperature (°C)	Conversion (%) ^[a]
1.5	132.2	120	54
1.5	132.2	130	83
2	176.2	130	89

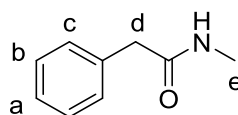
^[a] Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.43 (s, 2H, CH₂, product) and 3.46 (s, 2H, CH₂, acid).

General procedure 5.2



Carboxylic acid (1 equiv), *N,N'*-dimethylurea (2 equiv) and imidazole (0.2 equiv) were added to a carousel tube followed by octane (1 M), the reaction mixture was stirred at 130 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction mixture was then dissolved in ethyl acetate (15 mL) and extracted with sodium bicarbonate (3 x 20 mL). The aqueous layer were combined and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the desired product.

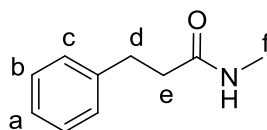
Synthesis of *N*-methyl-2-phenylacetamide 5.23¹⁷⁶



Following general procedure 5.2, phenylacetic acid (408.5 mg, 3 mmol), *N,N'*-dimethylurea (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as an off white

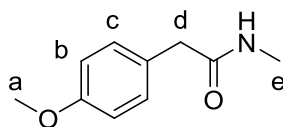
solid (310 mg, 2.07 mmol, 69% yield). Mp 51-53 °C [lit. mp 51 °C]. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.38 (m, 2H, c), 7.32-7.29 (m, 1H, a), 7.26 (d, $J=8.8$ Hz, 2H, b), 5.37 (br s, 1H, NH), 3.59 (s, 2H, d), 2.77 (d, $J=4.9$ Hz, 3H, e); ^{13}C NMR (125 MHz, CDCl_3) δ 171.6, 134.9, 129.5, 129.0, 127.3, 43.7, 26.4. HRMS calcd for $\text{C}_9\text{H}_{11}\text{NNaO}^+$: 172.0738; Found: 172.0754.

Synthesis of *N*-methyl-3-phenylpropanamide 5.24¹⁷⁷



Following general procedure 5.2, hydrocinnamic acid (450.5 mg, 3 mmol), *N,N'*-dimethylurea (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as an off white solid (329 mg, 2.01 mmol, 67% yield). Mp 58-60 °C [lit. mp 59-60 °C]. ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.28 (m, 2H, c), 7.22-7.19 (m, 3H, a+b), 5.41 (br s, 1H, NH), 2.97 (t, $J=7.6$ Hz, 2H, d), 2.78 (d, $J=4.9$ Hz, 3H, f), 2.47 (t, $J=7.8$ Hz, 2H, e); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 140.9, 128.4, 128.2, 126.1, 38.3, 31.7, 26.2. HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{NNaO}^+$: 186.0895; Found: 186.0912.

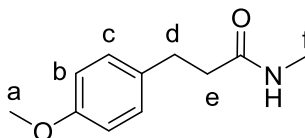
Synthesis of 2-(4-methoxyphenyl)-*N*-methylacetamide 5.25^{178,179}



Following general procedure 5.2, 4-methoxyphenylacetic acid (498.5 mg, 3 mmol), *N,N'*-dimethylurea (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as a yellow solid (441 mg, 2.40 mmol, 80% yield). Mp 89-90 °C [lit. mp 96-97 °C]. ^1H NMR (500 MHz, CDCl_3) δ 7.17 (d, $J=8.8$ Hz, 2H, c), 6.90 (d, $J=8.8$ Hz, 2H, b), 5.40 (br s, 1H, NH), 3.82 (s, 3H, a), 3.53 (s, 2H, d), 2.76 (d, $J=4.9$ Hz, 3H, e); ^{13}C NMR (125 MHz, CDCl_3) δ

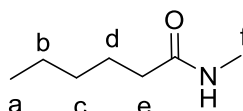
172.1, 158.8, 130.5, 126.8, 114.3, 55.2, 42.6, 26.4. HRMS calcd for $C_{10}H_{15}NO^+$: 180.1025; Found: 180.1073.

Synthesis of 3-(4-methoxyphenyl)-*N*-methylpropanamide 5.26¹⁸⁰

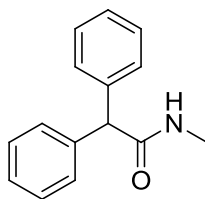


Following general procedure 5.2, 3-(4-methoxyphenyl)propionic acid (540.6 mg, 3 mmol), *N,N'*-dimethylurea (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as an off white solid (424 mg, 2.16 mmol, 72% yield). Mp 85-87 °C [lit. mp 87.5-88 °C]. 1H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, $J=8.8$ Hz, 2H, c), 6.83 (d, $J=8.8$ Hz, 2H, b), 5.37 (br s, 1H, NH), 3.79 (s, 3H, a), 2.91 (t, $J=7.6$ Hz, 2H, d), 2.77 (d, $J=4.9$ Hz, 3H, f), 2.44 (t, $J=7.8$ Hz, 2H, e); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 158.0, 132.9, 129.2, 113.8, 55.2, 38.6, 30.8, 26.2. HRMS calcd for $C_{11}H_{15}NNaO^+$: 216.1000; Found: 216.1036.

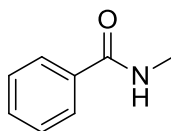
Synthesis of *N*-methylhexanamide 5.27¹⁸¹



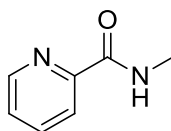
Following general procedure 5.2, hexanoic acid (408.5 mg, 3 mmol), *N,N'*-dimethylurea (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) were combined in octane (3 mL). Purification gave the desired product as a pale yellow oil (201 mg, 1.56 mmol, 52% yield). 1H NMR (500 MHz, $CDCl_3$) δ 5.52 (br s, 1H, NH), 2.81 (d, $J=2.9$ Hz, 3H, f), 2.16 (t, $J=7.3$ Hz, 2H, e), 1.66-1.60 (m, 2H, d), 1.36-1.26 (m, 4H, b+c), 0.89 (t, $J=7.2$ Hz, 3H, a); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 36.6, 31.5, 26.6, 26.4, 22.4, 13.9. HRMS calcd for $C_7H_{15}NNaO^+$: 152.1051; Found: 152.1075.

Synthesis of *N*-methyl-2,2-diphenylacetamide 5.28¹⁸²

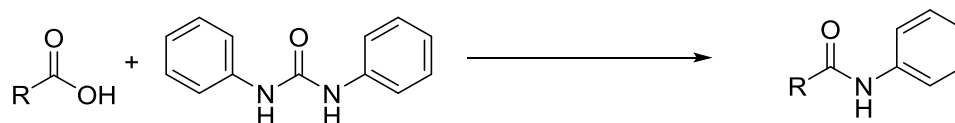
Following general procedure 5.2, diphenylacetic acid (636.7 mg, 3 mmol), *N,N'*-dimethylurea (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 29% conversion to the desired product, determined by analysis of ¹H NMR spectra by comparison of peaks at 4.97 (d, 2H, CH₂, product) and 5.11 (d, 2H, CH₂, acid).

Synthesis of *N*-methylbenzamide 5.29¹⁸³

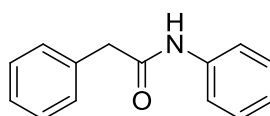
Following general procedure 5.2, benzoic acid (366.4 mg, 3 mmol), *N,N'*-dimethylurea (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 25% conversion to the desired product, determined by analysis of ¹H NMR spectra by comparison of peaks at 7.66-7.67 (d, 2H, CH, product) and 7.84-7.86 (d, 2H, CH, acid).

Synthesis of *N*-methylpicolinamide 5.30¹⁸⁴

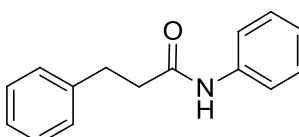
Following general procedure 5.2, 2-picolinic acid (369.6 mg, 3 mmol), *N,N'*-dimethylurea (528.7 mg, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 45% conversion to the desired product, determined by analysis of ¹H NMR spectra by comparison of peaks at 7.69 (d, 1H, CH, product) and 7.63 (d, 1H, CH, acid).

General procedure 5.3

Carboxylic acid (1 equiv), 1,3-dibenzylurea (2 equiv) and imidazole (0.2 equiv) were added to a carousel tube followed by octane, the reaction mixture was stirred at 130 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction mixture was then dissolved in ethyl acetate (15 mL) and extracted with sodium bicarbonate (3 x 20 mL). The aqueous layer were combined and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the desired product.

Synthesis of *N*,2-diphenylacetamide 5.31¹⁸⁵

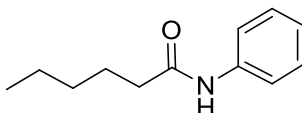
Following general procedure 5.3, phenylacetic acid (408.5 mg, 3 mmol), 1,3-dibenzylurea (1.27 g, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 42% conversion to the desired product, determined by analysis of ¹H NMR spectra by comparison of peaks at 3.71 (s, 2H, CH₂, product) and 3.67 (s, 2H, CH₂, acid).

Synthesis of *N*,3-diphenylpropanamide 5.32¹⁸⁶

Following general procedure 5.3, hydrocinnamic acid (450.5 mg, 3 mmol), 1,3-dibenzylurea (1.27 g, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL)

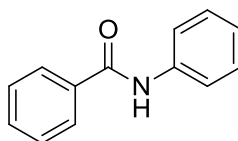
gave 33% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 3.07 (t, 2H, CH, product) and 3.03 (t, 2H, CH, acid).

Synthesis of *N*-phenylhexanamide 5.33¹⁸⁷



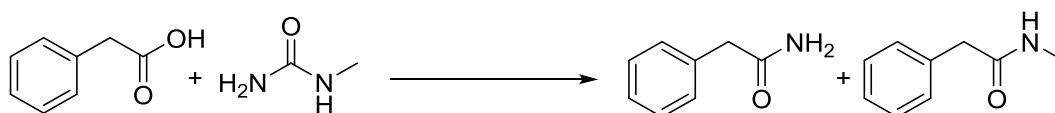
Following general procedure 5.3, hexanoic acid (376 μL , 348.5 mg, 3 mmol), 1,3-dibenzylurea (1.27 g, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 33% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 2.34 (t, 2H, CH_2 , product) and 2.30 (t, 2H, CH_2 , acid).

Synthesis of *N*-phenylbenzamide 5.34¹⁸⁸



Following general procedure 5.3, benzoic acid (366.4 mg, 3 mmol), 1,3-dibenzylurea (1.27 g, 6 mmol) and imidazole (40.9 mg, 0.6 mmol) in octane (3 mL) gave 9% conversion to the desired product, determined by analysis of ^1H NMR spectra by comparison of peaks at 7.89 (d, 2H, CH_2 , product) and 8.11 (d, 2H, CH_2 , acid).

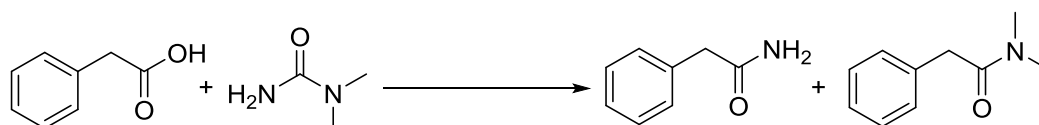
Reaction with *N*-methylurea (5.6 and 5.23)^{146,176}



Phenylacetic acid (136.2 mg, 1 mmol), *N*-methylurea (148.2 mg, 2.0 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1

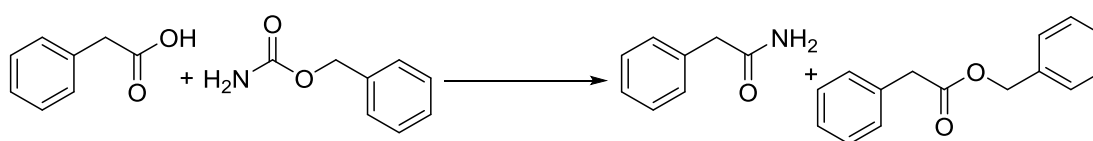
mL), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Conversions determined by analysis of ^1H NMR spectra by comparison of peaks at 3.40 (s, 2H, CH_2 , products) and 3.51 (s, 2H, CH_2 , acid). Conversions can be found in **Table 5.11**.

Reaction with *N,N*-dimethylurea (5.6 and 5.35)^{146,189}

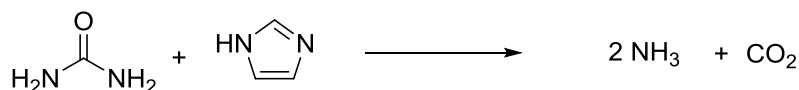


Phenylacetic acid (136.2 mg, 1 mmol) *N,N*-dimethylurea (176.2 mg, 2.0 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Conversions determined by analysis of ^1H NMR spectra by comparison of peaks at 3.38 (s, 2H, CH_2 , product 5.6), 3.67 (s, 2H, CH_2 , product 5.35) and 3.49 (s, 2H, CH_2 , acid). Conversions can be found in **Table 5.12**.

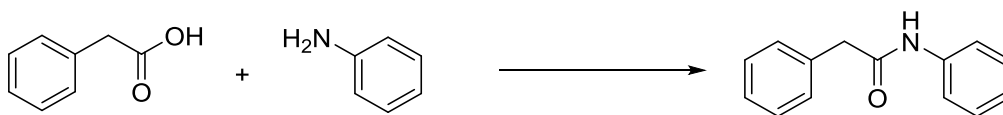
Reaction with benzylcarbamate (5.6 and 5.36)^{146,190}



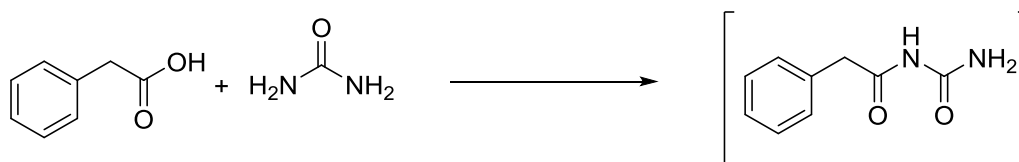
Phenylacetic acid (136.2 mg, 1 mmol), benzylcarbamate (302.3 mg, 2.0 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Conversions determined by analysis of ^1H NMR by comparison of peaks at 3.42 (s, 2H, CH_2 , product 5.6), 3.74 (s, 2H, CH_2 , product 5.36) and 3.59 (s, 2H, CH_2 , acid).

Decomposition of urea

Urea (90.1 mg, 1.5 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. 100 mg of material was recovered.

Reaction with aniline (5.31)¹⁸⁵

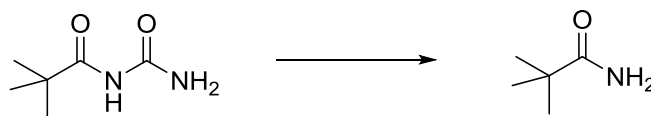
Phenylacetic acid (136.2 mg, 1 mmol), aniline (182 μL , 186.3 mg, 2.0 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Conversions determined by analysis of ^1H NMR spectra by comparison of peaks at 3.70 (s, 2H, CH_2 , product) and 3.60 (s, 2H, CH_2 , acid).

Determination of intermediate 5.39

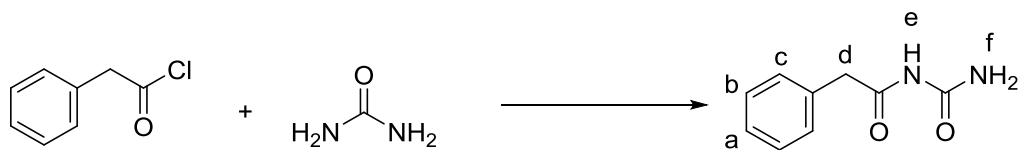
Phenylacetic acid (136.2 mg, 1 mmol), urea (60.1 mg, 1.0 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 120 °C for 6 hours. The reaction mixture was allowed to cool to room temperature and a sample was taken. Product presence identified by HRMS calcd for $\text{C}_9\text{H}_{10}\text{N}_2\text{NaO}_2^+$: 201.0640; Found: 201.0636.

Synthesis of *N*-carbamoylpivalamide 5.41¹⁵⁶

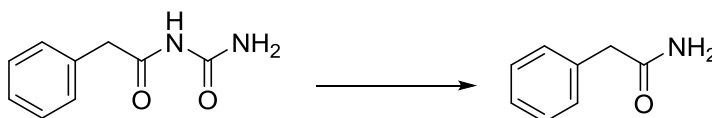
A solution of trimethylacetyl chloride (1.05 mL, 1.21 g, 10 mmol) in dry acetonitrile (20 mL) was added to a boiling solution of urea (2.4 g, 40 mmol) in dry acetonitrile (30 mL) under an atmosphere of argon, the reaction was heated at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction mixture was then dissolved in ethyl acetate (15 mL) and extracted with water (3 x 20 mL). The aqueous layer were combined and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the desired product as a white solid in 75 % yield (1.074 g, 7.5 mmol). Mp 147-149 °C [lit. mp 151-153 °C]. ¹H NMR (500 MHz, CDCl₃) δ 8.35 (br s, 2H, c), 5.64 (br s, 1H, b), 1.26 (s, 9H, a); ¹³C NMR (125 MHz, CDCl₃) δ 180.1, 155.3, 40.0, 26.3. HRMS calcd for C₆H₁₃N₂O₂⁺: 145.0977; Found: 145.0996.

Formation of amide 5.16 from *N*-Carbamoylpivalamide¹⁷²

N-carbamoylpivalamide (144.2 mg, 1 mmol), water (18 μL, 18.0 mg, 1.0 mmol) and imidazole (13.6 mg, 0.2 mmol) were added to a carousel tube followed by octane (1 mL), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Conversions can be found in **Table 5.13**. Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 1.07 (s, 9H, (CH₃)₃, product) and 1.15 (s, 9H, (CH₃)₃, acylurea).

Synthesis of phenylacetylurea 5.39¹⁹¹

A solution of phenylacetyl chloride (1.32 mL, 1.55 g, 10 mmol) in dry acetonitrile (20 mL) was added to a boiling solution of urea (2.4 g, 40 mmol) in dry acetonitrile (30 mL) under an atmosphere of argon, the reaction was heated at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The reaction mixture was then dissolved in ethyl acetate (15 mL) and extracted with water (3 x 20 mL). The aqueous layer were combined and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the desired product as a white solid in 43 % yield (771 mg, 4.3 mmol). Mp 218-220 °C [lit. mp 211-213 °C]. ¹H NMR (300 MHz, DMSO) δ 10.41 (br s, 1H, e), 7.69 (br s, 2H, f), 7.34-7.22 (m, 6H, a-b + f), 3.60 (s, 2H, d); ¹³C NMR (75.5 MHz, DMSO) δ 172.8, 154.0, 134.8, 129.3, 128.4, 126.9, 42.5. HRMS calcd for C₉H₁₁N₂O₂⁺: 179.0820; Found: 179.0816.

Synthesis of amide 5.6 from phenylacetylurea 5.6¹⁴⁶

Phenylacetylurea (89.1 mg, 0.5 mmol), water (9 μL, 9.0 mg, 0.5 mmol), hydrocinnamic acid (75.1 mg, 0.5 mmol) and imidazole (6.8 mg, 0.1 mmol) were added to a carousel tube followed by octane (0.5 mL), the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Conversions can be found in **Table 5.14**. Conversions determined by analysis of ¹H NMR spectra by comparison of peaks at 3.36 (s, 2H, CH₂, product) and 3.60 (s, 2H, CH₂, acylurea).

7 References

- (1) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.
- (2) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.
- (3) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109.
- (4) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049.
- (5) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914.
- (6) Xie, X.; Ni, G.; Ma, F.; Ding, L.; Xu, S.; Zhang, Z. *Synlett* **2011**, 955.
- (7) Tardiff, B. J.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *J. Org. Chem.* **2011**, *77*, 1056.
- (8) Ackermann, L.; Sandmann, R.; Song, W. *Org. Lett.* **2011**, *13*, 1784.
- (9) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.
- (10) Srivastava, V. P.; Yadav, D. K.; Yadav, A. K.; Watal, G.; Yadav, L. D. S. *Synlett* **2013**, *24*, 1423.
- (11) Raghuvanshi, D. S.; Gupta, A. K.; Singh, K. N. *Org. Lett.* **2012**, *14*, 4326.
- (12) Ullmann, F. *Berichte der deutschen chemischen Gesellschaft* **1903**, *36*, 2382.
- (13) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954.
- (14) Xi, Z.; Liu, F.; Zhou, Y.; Chen, W. *Tetrahedron* **2008**, *64*, 4254.
- (15) Niu, J.; Zhou, H.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2008**, *73*, 7814.
- (16) Wong, S. M.; Yuen, O. Y.; Choy, P. Y.; Kwong, F. Y. *Coord. Chem. Rev.* **2015**, *293-294*, 158.
- (17) Panda, N.; Jena, A. K. *Org. Chem.: Curr. Res.* **2015**, *4*, 1.
- (18) Hirano, K.; Miura, M. *Chem. Lett.* **2015**, *44*, 868.
- (19) Thapa, S.; Shrestha, B.; Gurung, S. K.; Giri, R. *Org. Biomol. Chem.* **2015**, *13*, 4816.
- (20) Biajoli, A. F. P.; Schwalm, C. S.; Limberger, J.; Claudino, T. S.; Monteiro, A. L. *Journal of the Brazilian Chemical Society* **2014**, *25*, 2186.
- (21) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.
- (22) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
- (23) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.
- (24) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141.
- (25) Yang, F.; Wu, Y.; Li, Y.; Wang, B.; Zhang, J. *Tetrahedron* **2009**, *65*, 914.
- (26) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740.
- (27) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236.
- (28) Semmelhack, M. F.; Seufert, W.; Keller, L. *J. Am. Chem. Soc.* **1980**, *102*, 6584.
- (29) Houghton, R. P.; Voyle, M.; Price, R. *J. Chem. Soc. Perk. Trans. 1* **1984**, 925.
- (30) Martinez, V.; Blais, J. C.; Bravic, G.; Astruc, D. *Organometallics* **2004**, *23*, 861.
- (31) Ruiz, J.; Astruc, D. *C.R. Acad. Sci., Ser. Ilc: Chim.* **1999**, *2*, 205.
- (32) Otsuka, M.; Endo, K.; Shibata, T. *Chem. Commun.* **2010**, *46*, 336.
- (33) Otsuka, M.; Yokoyama, H.; Endo, K.; Shibata, T. *Synlett* **2010**, 2601.
- (34) Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5756.
- (35) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

- (36) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
- (37) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.
- (38) Hine, J.; Linden, S. M.; Kanagasabapathy, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 1082.
- (39) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094.
- (40) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680.
- (41) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.
- (42) Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496.
- (43) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.
- (44) Yu, N.; Han, S.; Yu, H. *Tetrahedron* **2015**, *71*, 4665.
- (45) Zhang, Y.; Zhu, J.; Yu, N.; Yu, H. *Chin. J. Chem.* **2015**, *33*, 169.
- (46) Link, A.; Sparr, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5458.
- (47) Martínez-Castañeda, Á.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *J. Org. Chem.* **2012**, *77*, 10375.
- (48) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.
- (49) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 1112.
- (50) Chacko, S.; Ramapanicker, R. *J. Org. Chem.* **2015**, *80*, 4776.
- (51) Juhl, K.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1498.
- (52) Rajanarendar, E.; Nagi Reddy, M.; Govardhan Reddy, K.; Rama Krishna, S. *Tetrahedron Lett.* **2012**, *53*, 2909.
- (53) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3677.
- (54) Nagata, K.; Kuga, Y.; Higashi, A.; Kinoshita, A.; Kanemitsu, T.; Miyazaki, M.; Itoh, T. *J. Org. Chem.* **2013**, *78*, 7131.
- (55) Chacko, S.; Ramapanicker, R. *Tetrahedron Lett.* **2015**, *56*, 2023.
- (56) Díez, D.; Antón, A. B.; Peña, J.; García, P.; Garrido, N. M.; Marcos, I. S.; Sanz, F.; Basabe, P.; Urones, J. G. *Tetrahedron: Asymmetry* **2010**, *21*, 786.
- (57) Yang, H.; Wong, M. W. *Org. Biomol. Chem.* **2012**, *10*, 3229.
- (58) Sharma, A. K.; Sunoj, R. B. *J. Org. Chem.* **2012**, *77*, 10516.
- (59) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
- (60) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.
- (61) Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun.* **2009**, 5919.
- (62) Shen, Z.-L.; Cheong, H.-L.; Lai, Y.-C.; Loo, W.-Y.; Loh, T.-P. *Green Chem.* **2012**, *14*, 2626.
- (63) Bluet, G.; Campagne, J.-M. *J. Org. Chem.* **2001**, *66*, 4293.
- (64) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054.
- (65) Wang, J.-Q.; Dong, K.; Cheng, W.-G.; Sun, J.; Zhang, S.-J. *Catalysis Science & Technology* **2012**, *2*, 1480.
- (66) Shi, Z.; Glorius, F. *Chemical Science* **2013**, *4*, 829.
- (67) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.
- (68) Kiesewetter, M. K.; Scholten, M. D.; Kirn, N.; Weber, R. L.; Hedrick, J. L.; Waymouth, R. M. *J. Org. Chem.* **2009**, *74*, 9490.
- (69) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210.

- (70) Lohmeijer, B. G. G.; Pratt, R. C.; Leibfarth, F.; Logan, J. W.; Long, D. A.; Dove, A. P.; Nederberg, F.; Choi, J.; Wade, C.; Waymouth, R. M.; Hedrick, J. L. *Macromolecules* **2006**, *39*, 8574.
- (71) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6419.
- (72) Malkov, A. V.; Dufkova, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3674.
- (73) Chelucci, G.; Baldino, S.; Pinna, G. A.; Benaglia, M.; Buffa, L.; Guizzetti, S. *Tetrahedron* **2008**, *64*, 7574.
- (74) Murray, J. I.; Woscholski, R.; Spivey, A. C. *Chem. Commun.* **2014**, *50*, 13608.
- (75) Schwan, A. L. *Chemcatchem* **2015**, *7*, 226.
- (76) Zhang, M.; Jia, T.; Wang, C. Y.; Walsh, P. J. *J. Am. Chem. Soc.* **2015**, *137*, 10346.
- (77) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610.
- (78) Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.
- (79) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988.
- (80) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.
- (81) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3477.
- (82) Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871.
- (83) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.
- (84) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109.
- (85) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.
- (86) Vesely, J.; Rios, R. *Chemcatchem* **2012**, *4*, 942.
- (87) Palomo, C.; Oiarbide, M.; Lopez, R. *Chem. Soc. Rev.* **2009**, *38*, 632.
- (88) Dembek, A. A.; Fagan, P. J. *Organometallics* **1995**, *14*, 3741.
- (89) Cambie, R. C.; Clark, G. R.; Coombe, S. L.; Coulson, S. A.; Rutledge, P. S.; Woodgate, P. D. *J. Organomet. Chem.* **1996**, *507*, 1.
- (90) Semmelhack, M. F.; Chlenov, A.; Ho, D. M. *J. Am. Chem. Soc.* **2005**, *127*, 7759.
- (91) Walton, J. W.; Williams, J. M. J. *Chem. Commun.* **2014**.
- (92) Otsuka, M.; Yokoyama, H.; Endo, K.; Shibata, T. *Org. Biomol. Chem.* **2012**, *10*, 3815.
- (93) Gill, T. P.; Mann, K. R. *Organometallics* **1982**, *1*, 485.
- (94) Zelonka, R. A.; Baird, M. C. *J. Organomet. Chem.* **1972**, *44*, 383.
- (95) Trost, B. M.; Older, C. M. *Organometallics* **2002**, *21*, 2544.
- (96) Kundig, E. P.; Monnier, F. R. *Adv. Synth. Catal.* **2004**, *346*, 901.
- (97) Nesmeyanov, A. N.; Vol'kenau, N. A.; Bolesova, I. N. *Tetrahedron Lett.* **1963**, *4*, 1725.
- (98) Schmid, A.; Piotrowski, H.; Lindel, T. *Eur. J. Inorg. Chem.* **2003**, 2255.
- (99) Kundig, E. P.; Fabritius, C. H.; Grossheimann, G.; Romanens, P.; Butenschon, H.; Wey, H. G. *Organometallics* **2004**, *23*, 3741.
- (100) Chaplin, A. B.; Fellay, C.; Laurenczy, G.; Dyson, P. J. *Organometallics* **2007**, *26*, 586.

- (101) Fairchild, R. M.; Holman, K. T. *Organometallics* **2007**, *26*, 3049.
- (102) Fairchild, R. M.; Holman, K. T. *Organometallics* **2008**, *27*, 1823.
- (103) Gill, T. P.; Mann, K. R. *Inorg. Chem.* **1980**, *19*, 3007.
- (104) Gill, T. P.; Mann, K. R. *J. Organomet. Chem.* **1981**, *216*, 65.
- (105) Aranzaes, J. R.; Astruc, D. *Inorg. Chim. Acta* **2008**, *361*, 1.
- (106) Mori, S.; Mochida, T. *Organometallics* **2013**, *32*, 283.
- (107) Johnston, L. J.; Schepp, N. P. *Pure Appl. Chem.* **1995**, *67*, 71.
- (108) Etter, M. C.; Urbanczyklipkowska, Z.; Ziaebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415.
- (109) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.
- (110) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.
- (111) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.
- (112) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995.
- (113) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826.
- (114) Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606.
- (115) Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 8094.
- (116) Jiang, X.; Zhang, Y.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2009**, *11*, 153.
- (117) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754.
- (118) Kimmel, K. L.; Robak, M. T.; Thomas, S.; Lee, M.; Ellman, J. A. *Tetrahedron* **2012**, *68*, 2704.
- (119) Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. *Chemical Science* **2012**, *3*, 121.
- (120) Cao, X.-Y.; Zheng, J.-C.; Li, Y.-X.; Shu, Z.-C.; Sun, X.-L.; Wang, B.-Q.; Tang, Y. *Tetrahedron* **2010**, *66*, 9703.
- (121) Manzano, R.; Andrés, J. M.; Álvarez, R.; Muruzábal, M. D.; de Lera, Á. R.; Pedrosa, R. *Chem. Eur. J.* **2011**, *17*, 5931.
- (122) So, S. S.; Mattson, A. E. *J. Am. Chem. Soc.* **2012**, *134*, 8798.
- (123) So, S. S.; Oottikkal, S.; Badjic, J. D.; Hadad, C. M.; Mattson, A. E. *J. Org. Chem.* **2014**, *79*, 4832.
- (124) Hardman, A. M.; So, S. S.; Mattson, A. E. *Org. Biomol. Chem.* **2013**, *11*, 5793.
- (125) Kawazoe, S.; Yoshida, K.; Shimazaki, Y.; Oriyama, T. *Chem. Lett.* **2014**, *43*, 1659.
- (126) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259.
- (127) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647.
- (128) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817.
- (129) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
- (130) Hrdina, R.; Müller, C. E.; Wende, R. C.; Lippert, K. M.; Benassi, M.; Spengler, B.; Schreiner, P. R. *J. Am. Chem. Soc.* **2011**, *133*, 7624.
- (131) Tripathi, C. B.; Mukherjee, S. *J. Org. Chem.* **2012**, *77*, 1592.
- (132) Couch, E. D.; Auvil, T. J.; Mattson, A. E. *Chem. Eur. J.* **2014**, *20*, 8283.
- (133) Song, Q.; Feng, Q.; Yang, K. *Org. Lett.* **2014**, *16*, 624.
- (134) Chen, S. T.; Wu, S. H.; Wang, K. T. *Synthesis-Stuttgart* **1989**, 37.
- (135) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.

- (136) Bailén, M. A.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C. *Tetrahedron Lett.* **2000**, *41*, 9809.
- (137) Khalafi-Nezhad, A.; Mokhtari, B.; Soltani Rad, M. N. *Tetrahedron Lett.* **2003**, *44*, 7325.
- (138) Shteinberg, L. Y. *Russ. J. Org. Chem.* **2003**, *39*, 972.
- (139) Shteinberg, L. Y. *Russ. J. Appl. Chem.* **2005**, *78*, 1715.
- (140) Shteinberg, L. Y. *Russ. J. Appl. Chem.* **2006**, *79*, 1282.
- (141) Reddy, C. S.; Nagaraj, A.; Jalapathi, P. *Chin. Chem. Lett.* **2007**, *18*, 1213.
- (142) Reddy, C. S.; Raghu, M.; Nagaraj, A. *Indian Journal of Chemistry Section B-Organic Chemistry Including Medicinal Chemistry* **2008**, *47*, 315.
- (143) Tinnis, F.; Lundberg, H.; Adolfsson, H. *Adv. Synth. Catal.* **2012**, *354*, 2531.
- (144) Schnyder, A.; Beller, M.; Mehlretter, G.; Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311.
- (145) Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 5202.
- (146) Allen, C. L.; Burel, C.; Williams, J. M. J. *Tetrahedron Lett.* **2010**, *51*, 2724.
- (147) Takács, E.; Varga, C.; Skoda-Földes, R.; Kollár, L. *Tetrahedron Lett.* **2007**, *48*, 2453.
- (148) Veitch, G. E.; Bridgwood, K. L.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3623.
- (149) Cao, L.; Ding, J.; Gao, M.; Wang, Z.; Li, J.; Wu, A. *Org. Lett.* **2009**, *11*, 3810.
- (150) Ali, M. A.; Punniyamurthy, T. *Adv. Synth. Catal.* **2010**, *352*, 288.
- (151) Gowda, R. R.; Chakraborty, D. *Eur. J. Org. Chem.* **2011**, 2226.
- (152) Yamaguchi, K.; Kobayashi, H.; Oishi, T.; Mizuno, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 544.
- (153) Chen, H.; Dai, W.; Chen, Y.; Xu, Q.; Chen, J.; Yu, L.; Zhao, Y.; Ye, M.; Pan, Y. *Green Chem.* **2014**, *16*, 2136.
- (154) Chhatwal, A. R., Novel approaches to catalytic acyl transfer reactions, PhD, The University of Bath, Bath, 2015.
- (155) Stoddard, J. M.; Shea, K. J. *Thermochim. Acta* **2004**, *424*, 149.
- (156) Kaufmann, D.; Bialer, M.; Shimshoni, J. A.; Devor, M.; Yagen, B. *J. Med. Chem.* **2009**, *52*, 7236.
- (157) Bandna; Guha, N. R.; Shil, A. K.; Sharma, D.; Das, P. *Tetrahedron Lett.* **2012**, *53*, 5318.
- (158) Ueda, H.; Yoshida, K.; Tokuyama, H. *Org. Lett.* **2014**, *16*, 4194.
- (159) Kiritsy, J. A.; Yung, D. K.; Mahony, D. E. *J. Med. Chem.* **1978**, *21*, 1301.
- (160) Kumari, S.; Mishra, C. B.; Tiwari, M. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1092.
- (161) Beach, S. F.; Hepworth, J. D.; Sawyer, J.; Hallas, G.; Marsden, R.; Mitchell, M. M.; Ibbitson, D. A.; Jones, A. M.; Neal, G. T. *J. Chem. Soc. Perk. Trans. 2* **1984**, 217.
- (162) Yang, K.; Qiu, Y.; Li, Z.; Wang, Z.; Jiang, S. *J. Org. Chem.* **2011**, *76*, 3151.
- (163) Chen, D.; Yang, K.; Xiang, H.; Jiang, S. *Tetrahedron Lett.* **2012**, *53*, 7121.
- (164) Isley, N. A.; Linstadt, R. T. H.; Kelly, S. M.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2015**, *17*, 4734.
- (165) Kidwai, M.; Sapra, P.; Dave, B. *Synth. Commun.* **2000**, *30*, 4479.
- (166) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* **2014**, *16*, 2018.

- (167) Koltunov, Konstantin Y.; Walspurger, S.; Sommer, J. *Eur. J. Org. Chem.* **2004**, 2004, 4039.
- (168) Kitamura, M.; Miyagawa, S.; Okauchi, T. *Tetrahedron Lett.* **2011**, 52, 3158.
- (169) Tiemann, F. *Berichte der deutschen chemischen Gesellschaft* **1891**, 24, 2877.
- (170) Wu, H.; Kelley, C. J.; Pino-Figueroa, A.; Vu, H. D.; Maher, T. J. *Biorg. Med. Chem.* **2013**, 21, 5188.
- (171) Dewynter, G.; Hajri, A. H.; Toupet, L.; Montero, J. L. *Synth. Commun.* **2000**, 30, 2541.
- (172) Kita, Y.; Nishii, Y.; Onoue, A.; Mashima, K. *Adv. Synth. Catal.* **2013**, 355, 3391.
- (173) Huang, Y.; Chen, T.; Li, Q.; Zhou, Y.; Yin, S.-F. *Org. Biomol. Chem.* **2015**, 13, 7289.
- (174) Wu, X.-F.; Sharif, M.; Feng, J.-B.; Neumann, H.; Pews-Davtyan, A.; Langer, P.; Beller, M. *Green Chem.* **2013**, 15, 1956.
- (175) Knapp, S. M. M.; Sherbow, T. J.; Yelle, R. B.; Juliette, J. J.; Tyler, D. R. *Organometallics* **2013**, 32, 3744.
- (176) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2011**, 13, 5713.
- (177) Hanada, S.; Ishida, T.; Motoyama, Y.; Nagashima, H. *J. Org. Chem.* **2007**, 72, 7551.
- (178) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, 41, 3653.
- (179) Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, 135, 7304.
- (180) So, M.; Kotake, T.; Matsuura, K.; Inui, M.; Kamimura, A. *J. Org. Chem.* **2012**, 77, 4017.
- (181) Kita, Y.; Higuchi, T.; Mashima, K. *Chem. Commun.* **2014**, 50, 11211.
- (182) Hirner, S.; Somfai, P. *J. Org. Chem.* **2009**, 74, 7798.
- (183) Xia, Q.; Liu, X.; Zhang, Y.; Chen, C.; Chen, W. *Org. Lett.* **2013**, 15, 3326.
- (184) Cai, S.; Yu, X.; Chen, Z. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2006**, 65, 616.
- (185) Xie, P.; Xia, C.; Huang, H. *Org. Lett.* **2013**, 15, 3370.
- (186) Yao, H.; Tang, Y.; Yamamoto, K. *Tetrahedron Lett.* **2012**, 53, 5094.
- (187) Lee, S. I.; Son, S. U.; Chung, Y. K. *Chem. Commun.* **2002**, 1310.
- (188) Rattanaburi, P.; Khumraksa, B.; Pattarawarapan, M. *Tetrahedron Lett.* **2012**, 53, 2689.
- (189) Bradamante, S.; Pagani, G. A. *J. Chem. Soc. Perk. Trans. 2* **1986**, 1035.
- (190) Kim, H.; Lee, C. *Angew. Chem. Int. Ed.* **2012**, 51, 12303.
- (191) Taylor, J. D.; Trimitsis, G. B.; Hudlicky, T.; Wolfe, J. F. *J. Org. Chem.* **1973**, 38, 1236.